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SUBMISSION IN SUPPORT OF

DE-SCHEDULING MARIJUANA

CANNABIS DOES NOT MEET THE DEFINITION OF A CONTROLLED DANGEROUS SUBSTANCE -- AND NEVER HAS

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CANNABIS DOES NOT MEET THE DEFINITION OF A CONTROLLED DANGEROUS SUBSTANCE -- AND NEVER HAS

ARGUMENT

I. The Test For When a Substance is a Controlled Dangerous Substance and When It Is Not

The Director of the Division of Consumer Affairs is delegated the responsibility for determining which drugs to define as a Controlled Dangerous Substance (CDS) by placing the drug on any of the five schedules set forth in NJS 24:21-6 to 8.1. Pursuant to the statutory criteria, drugs are placed on one of the five schedules depending on the drug's potential for abuse and potential for physical or psychological dependence, relative to other drugs on the schedules. That is, drugs on schedule 4 have less potential for abuse than drugs on schedule 3; and drugs on schedule 5 have less potential for abuse than drugs on schedule 4. It follows that drugs that are not even scheduled as a CDS should have less potential for abuse and dependence than drugs on schedule 5. It should similarly follow that if cannabis has the same or less potential for abuse or dependence than other drugs that are not scheduled as CDS, that it too should not be a scheduled drug.

No one can deny that alcohol and tobacco can be abused, but they are expressly exempted from being placed on any schedule. Over-the-counter medications – acetaminophen, cough medicine, aspirin, and ibuprofen – have the demonstrated potential to be abused. Yet, not one of those substances is scheduled as a CDS.

Therefore, we contrast the scientific evidence for the potential abuse of four over-the-counter medicines as well as nicotine and alcohol with the scientific evidence for the potential

abuse of cannabis. Because the potential abuse of cannabis is less than those non-CDS substances, causes fewer and less serious physical or psychological dependence, and has an accepted medical use, cannabis should not be defined as, and never should have been scheduled as, a CDS.

II. Cannabis Has Less Potential to be Abused Than Common Over-the-Counter Medications And Substances That Are Not Classified as a CDS

In assessing a substance's potential for abuse, the Division must evaluate the physiological and psychological impact a drug may have on the individual. In this regard, the salient inquiries are: (1) does the drug cause damage to the health of the user, and (2) is the drug physically addictive. (Declaration of Dr. Carl Hart, ¶ 5.)[1]

Scientific research overwhelmingly concludes that cannabis, unlike the over-the-counter medications described below, causes *no* illness, disease, or organ damage, and is *not* physically addictive. When compared to other substances which are legally distributed in the open market, cannabis is proven to be far less harmful, and its continued presence as a CDS is scientifically erroneous.

A. Cannabis has less potential to cause damage to the health of the user than many over the counter medicines.

Acetaminophen: The commonly-used substance called acetaminophen (e.g., Tylenol) is the leading cause of acute liver failure in the United States. In fact, acetaminophen *hepatotoxicity* results in more calls to poison control centers than the overdose of any other pharmacological substance. (Declaration of Dr. Phillip A. Denney ¶ 11.)[2] The National Institutes of Health has

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[1] Exhibit 1, filed in USA v. McDonald, 3:14-CR-53 in the United States District Court for the District of Nebraska. Hereafter, (Hart Decl. w citation of the paragraph where the specific information described may be found).

[2] Exhibit 2, filed in USA v. McDonald; 3:14-CR-53 in the United States District Court for the District of Nebraska. Hereafter, (Denny Decl. w citation of the paragraph where the specific information described may be found).

found that "Acetaminophen overdose is one of the most common poisonings world wide."[3] The danger is so great that Johnson & Johnson, makers of Tylenol, recently modified their label to try to reduce the number of accidental acetaminophen overdoses that occur each year.[4] On August 2, 2013, the U.S. Food and Drug Administration (FDA) released a statement warning that overuse of acetaminophen could cause serious rashes and even death.[5] It has long been noted that acetaminophen use can cause upper gastrointestinal complications such as bleeding, kidney damage, and even increased risk of blood cancer. (*Id.*; *see also* Denney Decl. ¶ 9.) Despite the significant potential for harm caused by this substance, it is not classified as a CDS and is entirely excluded from the scheduling scheme.

Dextromethorphan: Dextromethorphan (DXM or DM) is distributed and used as a popular cough syrup, although the substance can result in drowsiness and hallucinations even at recommended doses, as well as euphoria and black outs at high doses. (Denney Decl. ¶ 12.) The DEA has reported that abuse of DXM for its dissociative effects is gaining popularity and is of "particular concern of use by teenagers and young adults."[6]

Abuse of DXM is exceedingly dangerous when used in conjunction with alcohol or other drugs and can even result in death. (*Id.*) Despite the current medical science which establishes that

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[3] *See*, National Institutes of Health (NIH) website printout, entitled "Acetaminophen Overdose," located online at http://www.nlm.nih.gov/medlineplus/ency/article/002598.htm.

[4] *See*, Cable News Network (CNN) article entitled "New Tylenol cap will have warning label," dated August 30, 2013, located online at http://www.cnn.com/2013/08/29/health/tylenol-cap-warning/.

[5] *See*, FDA website printout, entitled "FDA Warns of Rare Acetaminophen Risk," issued August, 2013, located online at http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM363067.pdf.

[6] *See*, Drug Enforcement Administration (DEA), Drug & Chemical Evaluation Sheet for Dextromethorphan, located online at http://www.deadiversion.usdoj.gov/drug_chem_info/dextro_m.pdf.]

DXM has a greater potential for abuse than marijuana, DXM is explicitly excluded from the list of controlled substances.

Acetylsalicylic acid: Acetylsalicylic acid, or aspirin, is a nonsteroidal anti- inflammatory drug used for temporary pain relief and fever reduction. At recommended doses, aspirin may cause Dyspepsia, mild to life-threatening gastric blood loss, Reye's Syndrome (a childhood disease related to aspirin use), and significant allergic reactions. (Denney Decl. ¶ 15.) At toxic doses, the danger of life-threatening gastrointestinal bleeding also increases. *Id.* Toxic doses of aspirin can also cause Salicylism, a condition with symptoms including tinnitus, deafness, nausea, abdominal pain, flushing and fever. *Id.* Despite those significant potential risks, aspirin is not a scheduled CDS.

Ibuprofen: Like aspirin, ibuprofen is a nonsteroidal anti-inflammatory pain reliever and fever reducing over-the-counter medication. Also, like aspirin, ibuprofen use may be extremely harmful even at recommended doses. Studies show chronic use causes hypertension and possibly myocardial infarction, renal impairment, broncho spasm, and esophageal ulceration. It is important to note that ibuprofen use can actually cause death in limited instances. Further, this substance is often combined with sedatives, such as diphenhydramine, the ingredients in Motrin PM, and therefore causes drowsiness. (Denney Decl. ¶ 16-17.) Despite those significant risks of harm, ibuprofen also is not a scheduled CDS.

Cannabis: Medical science evidences that cannabis has a notably low potential for abuse. Compared to the over-the-counter substances listed above, cannabis has the lowest potential for abuse, as it is impossible to die from an overdose; further, no studies have proven that the use of cannabis causes harms similar to those caused by the use of common over-the-counter medications, even at their recommended dosages. (Denney Decl. ¶ 8, 12, 15, 20.)

Unlike those OTC's, there have been *zero* documented deaths caused by an overdose of cannabis in the United States, and, as noted by Dr. Denney, an overdose would be impossible based on the physiological properties of the plant. (Denney Decl. ¶ 2.)

The distinction between harms caused by the four over-the-counter medications described above and marijuana is demonstrated in the following table which compares the Therapeutic Index of the above OTCs with cannabis. The Therapeutic Index is a number that denotes the relationship between a therapeutic and a toxic dose of a substance – that is, how many times the therapeutic dose results in toxic levels. A lower therapeutic index means that there is a narrower difference between a safe therapeutic dose and a toxic dose, and therefore higher numbers are preferable.

Substance	**Therapeutic Index**
Cannabis	< 1,000 - 40,000
Dextromethorphan: (cough meds)	< 10
Acetaminophen	<3
Aspirin	<5
Ibuprofen	< 20

The Therapeutic Index for marijuana really is theoretical because there have been no substantiated deaths nor life threatening harm caused by the overdose of cannabis, and it would be impossible to ingest 1,000 to 40,000 times the therapeutic level within the time required to test its impact. *Id.*

In addition, unlike the critical damage to the body's internal organs caused by the over-the-counter medications described above, studies have proven cannabis not only does not cause such damage, but also suggest that, in some instances, cannabis has a curative effect. (Denney Decl. ¶ 28.)

The Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) describes the effects of prescription and over-the-counter drugs as far greater than those articulated in the same section for cannabis: "Psychotic syndromes may be temporarily experienced in the

context of anticholinergic, cardiovascular, and steroid drugs, as well as use of stimulant-like and depressant-like prescription or *over-the-counter drugs*. Temporary but severe mood disturbances can be observed with a wide range of medications, including steroids, antihypertensives, disulfrum, and any prescription or *over-the-counter* depressant or stimulant-like substances." (Emphasis added). *Id.* 548 under the heading "Features".

Finally, concerns regarding the use of cannabis and driving can be and are being controlled much the way they are for alcohol and prescriptions medications. (Denney Decl. ¶ 31.) It is, however, important to note that recently the National Highway Traffic Administration (NHTSA) published the first large-scale case-control study ever conducted in the United States to assess the crash risk associated with both drugs and alcohol use by drivers--ultimately it was determined that drivers who test positive for the presence of THC in blood are *no* more likely to be involved in motor vehicle crashes than are *drug-free* drivers[7]. Denney Decl. ¶ 31.

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[7] "We (the state of Colorado) have not experienced any significant issue as a result of legalization. ... We have actually seen an overall decrease in DUI's since legalization. So, the short answer is: There has been no increase since the legalization of marijuana here." *Comments from Larry Wolk, Chief Medical Officer of the Colorado Department of Public Health, October 23, 2017*

"We found no significant association between recreational marijuana legalization in Washington and Colorado and subsequent changes in motor vehicle crash fatality rates in the first three years after recreational marijuana legalization. ... [W]e also found no association between recreational marijuana legalization and total crash rates when analyzing available state-reported nonfatal crash statistics." *Crash fatality rates after recreational marijuana legalization in Washington and Colorado, Journal of the American Public Health Association, 2017*

"In monitoring the impacts of recreational marijuana legalization in Washington State, government researchers report that there was no trend identified in the percentage of drivers testing positive for marijuana (either marijuana only or marijuana in combination with other drugs/alcohol) for those involved in traffic fatalities and who were tested for drugs or alcohol. *The Marijuana Policy Gap and the Path Forward, Congressional Research Service, 2017*

"To this point, as a result of legalization, we haven't seen a large spike or epidemic of ... THC driving [in Oregon]." *Marijuana Legalization Hasn't Increased Traffic Fatalities In Oregon, Oregon Public Broadcasting, March 9, 2017*

"[O]n average, medical marijuana law states had lower traffic fatality rates than non-MML states. .... Medical marijuana laws are associated with reductions in traffic fatalities, particularly pronounced among those aged 25 to 44 years. ... It is possible that this is related to lower alcohol-impaired driving behavior in MML-states." *US Traffic Fatalities, 1985-2014, and Their Relationship to Medical Marijuana Laws, Journal of the American Public Health Association, 2016*

When compared relative to the potential harm that those other drugs can cause the human body, it is clear that cannabis poses a lesser risk of harm or abuse.

B. Cannabis has less potential to cause damage to the health of the User And creates lLesser dependency than alcohol and/or tobacco

Each year it is estimated that there are 400,000 to 500,000 excess deaths from tobacco and 100,000 to 200,000 excess deaths from alcohol. (Denny Decl. ¶23). Based on that fact alone, tobacco and alcohol cause far more damage to the health of a user than cannabis does. Moreover, it has long been established that marijuana is not physically addictive, and there are minimal, if any, withdrawal symptoms associated with the cessation of marijuana use. (Denney Decl. ¶ 4.)

The current data indicates just under 9% of those who have experimented with cannabis have become dependent compared to 32% for alcohol and 22.7% for nicotine. Cannabis dependence liability is less than half of cocaine and alcohol and thirteen percent of nicotine. (Hart Decl. ¶6)[8] "Further, from my own research in human test subjects indicates that symptoms of marijuana withdrawal are relatively minor when compared to withdrawal symptoms experienced by those discontinuing use of other substances, including alcohol…" (*Id.* at ¶7). "In summary, although few marijuana users develop dependence, some do. But they appear to be less likely to do so than users of other drugs (including alcohol and nicotine)." (*Id.* at ¶10)

The Diagnostic and Statistical Manual of Mental Disorders (DSM) (Fifth Ed.) clearly demonstrates the relatively low potential for abuse of cannabis. In fact, it appears the criteria indicative of Cannabis Use Disorder are most similar to that of Caffeine Use Disorder; however,

[8] A 1994 assessment agreed that cannabis had only a 9% dependency rate, but found tobacco had a 32 % addiction rate. Anthony JC, Warner LA, Kessler RC (1994), Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology 2*(3):244-268.

remarkably, the Functional Consequences of Caffeine Intoxication can be fatal (*Id.* 505); not so for cannabis. (Denney Decl. ¶ 45.)

III. Cannabis Undeniably Has an Accepted Use in the Medical Profession

In this State, cannabis has an accepted medical use. Therefore, Cannabis can not fall within the definition of a schedule I controlled dangerous substance, which is a drug that (1) has high potential for abuse; and (2) has no accepted medical use in treatment in the United States; or lacks accepted safety for use in treatment under medical supervision. NJSA 24:21-5.

The Governor has announced New Jersey's position that cannabis has an accepted medical use in no uncertain terms -- in the "whereas" clauses to Executive Order # 6 promulgated on January 23, 2018: "scientific studies demonstrate that the medical use of marijuana has proven to be an effective treatment for patients suffering from painful, debilitating, and often chronic medical conditions;" "my administration is committed to fulfilling the intent, promise, and potential of the New Jersey Compassionate Use Medical Marijuana Act by providing patients in New Jersey with a well-functioning and effectively administered medical marijuana program that best serves their medical needs."[9]

Of course, medical cannabis has an accepted use throughout the world, and has for thousands of years. National Academy of Science Report, "The Health Effects of Cannabis and Cannabinoids" released in January of 2017 confirmed that there was evidence (divided among categories of "conclusive", "substantial", "moderate" and "limited") that cannabis was effective in treatment of chronic pain in adults, chemotherapy induced nausea and vomiting, multiple sclerosis spasticity symptoms, improving short-term sleep outcomes for those with destructive

[9] Governor Phillip Murphy's Executive Order # 6 promulgated on January 23, 2018, attached as Exhibit 3.

sleep apnea syndrome, fibromyalgia, Tourette syndrome, increasing appetite and decreasing weight loss associated with HIV/AIDS, post-traumatic stress disorder, and anxiety symptoms[10].

Dr. Lester Grinspoon of the Harvard Medical School has written that the medicinal use of cannabis has created another category of the practice of medicine. In addition to allopathic medicine (traditional western medicine), osteopathic and homeopathic, there is now a legitimate category of medicine known as cannabinopathic medicine. Dr. Grinspoon points out that cannabis as medicine was well known in Asia for thousands of years, before W.B. O'Shaughnessy, a professor of medicine in India, returned to England in the mid-nineteenth century. "Shortly after O'Shaughnessy introduced cannabis as a new medicine, modern Western medicine (allopathic) signaled its acceptance when it was entered into the various Western pharmacopeia in the mid-19th century." Dr. Grinspoon concluded, "There is now little question about [cannabis's] safety. It has been used for thousands of years by millions of people with very little evidence of significant toxicity. Similarly, no further double-blind studies are needed to prove marijuana's efficacy. Any astute clinician who has some knowledge of the accumulated clinical experience of patients who have used marijuana as a medicine knows that it is efficacious to some degree for many people with various symptoms and syndromes." [11] (Emphasis added)

The following Medical Organizations have accepted cannabis as medicine which provides useful treatment.

Addiction Science Forum—2009
AIDS Action Council—1996
American Academy of Family Physicians—1989,1995
American Academy of HIV Medicine—2003

[10] The Report is 488 pages, including the Appendix. A summary of that report is, included in the Appendix as Exhibit 4.

[11] "Cannabinopathic Medicine" by Lester Grinspoon, MD (An update to "Whither Medical Marijuana" published by Contemporary Drug Problems, volume 27), attached as Exhibit 5.

American College of Physicians—2008
American Medical Association's Council on Scientific Affairs—2001
American Medical Students Association—1993
American Nurses Association—2003
American Preventive Medical Association—1997
American Public Health Association (APHA)—1995
Association of Nurses in AIDS Care—1999
California Medical Association—1994
California Nurses Association—1995
Consumers Reports Magazine—1997
Doctors for Cannabis Regulation-2016
Federation of American Scientist—1994
Florida Medical Association—1997
Hawaii Nurses Association—1999
HIV Medicine Association—2006
Lancet (UK)—1995, 1998
Medical Society of the State of New York—2004
Multiple Sclerosis California Action Network (MS-CAN)—1996
National Association for Public Health Policy—1998
New England Journal of Medicine—1997
New Hampshire Medical Association—2003
New Jersey Nurses Association—2002
New York State Association of County Health Officials—2003
Rhode Island Medical Society—2004
The American Federation of State, County and Municipal Employees (AFSCME)—2006
Virginia Nurses Association—1994, 2004[12]

Nor is it irrelevant that 30 of the 50 States plus the District of Columbia have recognized that cannabis has having an accepted medical use by creating Medical Cannabis programs.

IV. The Discovery of the Endocannabinoid System Proves Cannabis Is Not a Controlled Dangerous Substance Which Should Now Be De-Scheduled

A substance that is virtually identical to what the human body produces in order to maintain health cannot rationally be classified as a Controlled Dangerous Substance. The cannabinoids found in the marijuana plant are virtually identical to cannabinoids produced by the human body.

Science has now explained why cannabis is effective medicine for so many seemingly unrelated health issues. The explanation is revealed by the discovery of the endocannabinoid system (ECS)

[12] The Patients Out of Time website (www.medicalcannabis.com) lists approximately 200 organizations that have proclaimed cannabis has effective medical use. The cited organizations were drawn from that list.

in our bodies. This profound discovery has proceeded in stages. The initial event occurred in 1988 with the discovery of cannabinoid receptors in the brain (designated now as CB1 receptors). In 1992, Dr. Raphael Mechoulam identified the first endocannabinoid (Anandamide) produced by the human body, which activates the CB1 receptors. In 1993, cannabinoid receptors were found in the immune system (CB2 receptors). In 1995, the second endocannabinoid (2-Arachidonoylglycerol -- 2-AG for convenience) was identified. By 2000, researchers and scientists reached agreement that the ECS functions throughout the body. Its primary purpose is to maintain homeostasis (balance; effective functioning) within the human body.

Interestingly, none of these cannabinoid receptors are found in the brain stem. The brain stem regulates vital functions such as breathing and heartbeat. Opioid receptors are found in the brain stem, which is why overdoses of opioids cause respiratory suppression and subsequent cardiac arrest. The absence of cannabinoid receptors in the brain stem explains why there has never been a death from cannabis overdose.

Phytocannabinoids – the cannabinoids in the cannabis plant – are recognized by the endocannabinoid receptors and enhance their function. The phytocannabinoids are virtually identical to the endocannabinoids and mimic their activity. Thus, if the ECS is compromised, the phytocannabinoids can "signal the body to make more endocannabinoids and build more cannabinoid receptors"[13]. This leads to the theory that the ingestion of phytocannabinoids can actually act as a preventative of disease in addition to being a safe treatment for a wide range of illness and disorders.

[13] Sulak, "Introduction to the Endocannabinoid System", attached as Exhibit 6.

CONCLUSION

For all the reasons above, cannabis should be de-scheduled.

PASHMAN STEIN WALDER HAYDEN
A Professional Corporation

Dated: April 17, 2018 By: */s/ Alan Silber*
ALAN SILBER

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF IOWA
DAVENPORT DIVISION

UNITED STATES OF AMERICA, Plaintiff, vs. AEDAN MACDONALD, *et al.* Defendants.	No. 3:14-cr-53 **DECLARATION OF PHILIP A. DENNEY, M.D. IN SUPPORT OF DEFENDANT'S MOTION TO DISMISS**

I, PHILIP A. DENNEY, M.D. declare as follows:

I am a retired physician who was first licensed to practice medicine in the State of California in 1977. I attended medical school at the University of Southern California after serving in the United States Navy. Since graduation I have practiced Family, Emergency and Occupational Medicine. I have never been disciplined by the Medical Board, nor have my hospital privileges been revoked, suspended or restricted. I have been involved in the emerging field of cannabis medicine since 1999, and have practiced in Loomis, Redding, Lake Forrest, Oakland and Sacramento, California. I retired from active practice in 2010, but have continued to study the developments in medical cannabis scientific/medical research.

I have qualified to testify as an expert witness regarding the medical use of cannabis in at least 21 counties throughout California as well as in the District Court for the Eastern District of California. I have also testified before the California Medical Board regarding medicinal cannabis. I am a founding member of the Society of Cannabis Clinicians, and have been active in the development of policy regarding cannabis as medicine in El Dorado County, and in this regard have been asked to consult with Judges, District Attorneys, and law enforcement officers about the medical use of cannabis. I also

testified before the Arkansas State Legislature regarding the implementation of cannabis as medicine laws and policies, and have been consulted by members of the campaign to legalize the medical use of cannabis in the state of Montana.

While cannabis is considered a Schedule I Controlled Substance under the federal law, the overwhelming majority of current medical research contradicts such a classification. A Schedule I "Controlled Substance" is defined in *21 U.S.C. section 812(b)(1)* as follows:

(A) The drug or other substance has a high potential for abuse;

(B) The drug or other substance has no currently accepted medical use in treatment in the United States;

© There is a lack of accepted safety for use of the drug or other substance under medical supervision.

For the reasons provided in this declaration, and those which may be presented at hearing, it is my professional medical opinion that cannabis has a low potential for abuse, is currently accepted and used medically to treat multiple serious medical conditions, and has been safely used under medical supervision for nearly sixteen years in the State of California and elsewhere. Moreover, the safety and medical efficacy of cannabis far exceeds that of many other prescribed and over-the-counter (OTC) medications, in that it is less toxic, possesses a low abuse potential, and is incapable of causing lethal overdose.

Based on my training, experience, and review of pertinent human-subject clinical trials and other research conducted in accord with accepted principles and methodologies,[1] I have formed the opinion that cannabis fails to meet the criteria for inclusion in Schedule I of the Controlled Substances Act.

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[1] Attached hereto, and incorporated by reference, is an Addendum which highlights studies which I believe are of great significance to the issue before this Court, and therefore, exclude pre-clinical trials, animal studies and anecdotal evidence.

I attest to the following in support of this opinion:

Cannabis and Potential for Abuse

1. In determining whether a substance has a high potential for abuse, a physician assesses both the physical and psychological effect of the drug. It is my opinion that cannabis has minimal potential for physical abuse, and low potential for psychological abuse.

2. Cannabis is a non-toxic, non-lethal substance. There have been *no* confirmed deaths resulting from an overdose of marijuana and, in fact, based on the physiological properties of the plant, an overdose would be, as a practical matter, impossible.

3. Many over-the-counter medications pose inherent health risks, and some are toxic even when used as recommended. As detailed, *infra*, adverse effects and/or overdoses can result in permanent major organ failure and death.

4. Unlike many drugs, including some over-the-counter (OTC) medications, cannabis has a notably low abuse potential, and cessation causes minimal physiological symptoms of withdrawal.

5. While some studies have identified an association between cannabis use and psychosis, none have identified a causal relationship between cannabis use and mental illness in otherwise healthy individuals not already predisposed to these conditions. The association between marijuana use and mental illness is most likely not one of causation, but rather reflects the tendency of those in psychological distress to self-medicate, and the fact that diseases such as schizophrenia and bipolar disorder generally manifest themselves in late adolescents and early adulthood, which is the same age during which individuals are most likely to use illegal drugs. Further, the hypothesis that marijuana may cause the onset of these serious mental illnesses is contradicted by the evidence that worldwide rates of schizophrenia have largely remained static despite dramatically changing rates of cannabis use by various populations over multiple generations. In fact, through my training and experience I have found

cannabis has been successfully used to treat psychological disorders such as anxiety, depression and PTSD in a number of patients who have not found other treatments sufficiently helpful.

6. The psychological effects of cannabis are similar to those of many OTCs. For instance, relaxation, euphoria, and sedation are frequently reported with use of THC (the psychoactive cannabinoid in marijuana). These same symptoms are common with cough medicines, antihistamines, nausea medication, and many others.

7. Clinical trials and case studies on human subjects support my opinion that cannabis is not only an effective medicine, but one with fewer and less serious side effects than many medications in common use. Examples discussed in detail herein include:

A. Acetaminophen (OTC analgesics Tylenol)

B. Dextromethorphan: (OTC cough medications)

C. Acetylsalicylic Acid (aspirin)

D. Ibuprofen (Advil and Motrin)

A. Acetaminophen: Common Brand Name, Tylenol

8. Acetaminophen, is a widely used temporary pain reliever and fever reducer. The substance carries a warning of the potential for severe liver damage even at relatively low doses. For instance, the Physician's Desk Reference (PDR) for Nonprescription Drugs warns that sever liver damage may occur if a patient takes more than 6 650 mg caplets in a 24 hour period, yet the recommended dose for adults is 2 650 mg caplets every 8 hours. Accordingly even small amounts over the recommended dose could cause serious harm.

9. Other side effects of this substance include upper gastrointestinal complications such as bleeding, and kidney damage. There is also some evidence that chronic users of acetaminophen may

have a higher risk of developing blood cancer. For even modest users of alcohol, these effects are more pronounced.

10. The FDA issued a warning on August 2, 2013, that this substance could cause a serious skin reaction which could be fatal. Additionally, a 2010 study suggests that infertility of adults whose mother used acetaminophen while pregnant could be the result of such use.

11. Significantly, acetaminophen hepatotoxicity is the most common cause of acute liver failure in the United States, and results in more calls to poison control centers than the overdose of *any* other pharmacological substance. Even if treated, an overdose can lead to liver failure within days. While the most important toxic effect of acetaminophen is hepatic necrosis leading to liver failure after an overdose, there are also reported cases of renal failure after overdose. On January 14, 2014, the FDA issued a recommendation to health care professionals to discontinue prescription combination drug products with more than 325 mg of acetaminophen in order to protect consumers from liver damage. In April of 2014, the FDA had to "remind" health care professionals to stop dispensing prescription combination drug products with more than 325 mg of acetaminophen because they were "no longer considered safe by the FDA."

B. Dextromethorphan Common brand names: Benylin, Nyquil and Robitussin

12. Dextromethorphan, also referred to as DXM or DM, is used to temporarily relieve cough due to minor throat and bronchial irritation. DXM is widely abused as it acts as a dissociative hallucinogen. Even at recommended doses it can cause nausea, drowsiness, dizziness, difficulty breathing, skin rashes, and hallucinations. At higher doses DXM can result in hallucinations, dissociation, vomiting, hypotenstion, hypertension, tachycardia, diarrhea, muscle spasms, sedation, euphoria, black outs, and loss of sight.

13. In addition, DXM can have serious heath consequences when taken at the same time or shortly after taking certain prescription medication used to treat depression, psychiatric conditions, and Parkinson's Disease.

14. Because this product simulates the effects of alcohol, it may be subject to abuse and addiction in the same way, and has resulted in overdose.

C. Acetylsalicylic Acid

15. Acetylsalicylic Acid, or aspirin, is a nonsteroidal anti-inflammatory drug used to temporarily relieve minor aches and pains, and to reduce fever. Even recommended doses commonly cause Dyspepsia and mild to life-threatening gastrointestinal blood loss, and allergic reactions such as hives, shock, facial swelling and asthma. Reye's syndrome, which is a rare but commonly fatal childhood illness, is a known risk to the use of aspirin. Further, toxic doses of this substance can cause tinnitus, deafness, nausea, abdominal pain, flushing and fever.

D. Ibuprofen: Common brand names include Advil and Motrin.

16. Ibuprofen is a nonsteroidal anti-inflammatory used for temporary pain relief and fever reduction. It is common for those taking therapeutic doses to suffer nausea, dyspepsia, gastrointestinal ulcerations and bleeding, raised liver enzymes, diarrhea, constipation, epistaxis, headache, dizziness, rash, salt and fluid retention, and hypertension.

17. Ibuprofen may cause a severe allergic reaction, causing hives, facial swelling, asthma, shock, skin reddening, rash and blisters. Some studies indicate that chronic use of Ibuprofen may cause hypertension and possibly myocardial infarction, renal impairment, broncho spasm, and esophageal ulceration. Significantly, it can also be fatal to some asthmatics.

18. Also, when combined with diphenhydramine, the ingredients in Motrin PM, a patient is warned not to operate a motor vehicle, as it will cause drowsiness.

* * *

19. Cannabis has not been linked to any of the serious side-effects associated with the above described OTC medications.

20. A widely used measure of a drug's harmful effect is the Therapeutic Index, or Ratio. This refers to the relationship between toxic and therapeutic dose, and is calculated by determining the ratio of the dose that produces toxicity (TD50) and dividing it by that which produces a clinically desired or effective response (ED50), in 50% of the subjects. A low therapeutic index heightens the drug's potential to be lethal. Some over-the-counter medications have a low Therapeutic Index, meaning the difference between the therapeutic and toxic dose is very small. For example, the estimated Therapeutic Index for acetaminophen is less than 3 and may be lower with alcohol use. The Therapeutic Index for aspirin is less than 5 and bleeding can occur even at the recommended dose. In contrast, the Therapeutic Index for cannabis is estimated to be between 1,000 and 40,000.[2]

21. The following table compares the Therapeutic Index of above OTCs with cannabis:

Substance	**Therapeutic Index**
Cannabis	1000 - 40,000
Dextromethorphan: (cough meds)	< 10
Acetaminophen	< 3
Aspirin	< 5
Ibuprofen	< 20

[2] It should be noted that, since there are no confirmed deaths nor life threatening harm caused by the overdose of marijuana, the Therapeutic Index for cannabis is theoretical. Also, because it would be impossible to ingest 1,000 to 40,000 times the therapeutic dose within the time required to test its impact, practically the Therapeutic Index in the case of marijuana ingestion does not exist.

22. I have chosen to make the comparison between cannabis and over-the-counter medications to demonstrate the benign nature of the former; however, the obvious should be noted: the potential for abuse associated with prescription medications is far greater than that posed by OTCs, let alone cannabis. A comparison between cannabis and prescription medications demonstrates compelling evidence that the former is safer and can be more effective in treating illnesses. For example, the Therapeutic Index for many prescription medications such as psychiatric medications, opiates, cardiac medications, etc., are less than 10. The mortality rate for each of many prescription medications is significant. Furthermore, known side effects of prescription medications are far to numerous to here articulate. I can think of no prescription medication which has fewer potential harmful side effects than cannabis.

23. Finally, an evaluation of cannabis is not complete without comparing it to alcohol and tobacco. Tobacco being the more toxic substance, and alcohol a close second. The excess death rate associated with use and abuse of these substances is staggering. The Center for Disease Control and Prevention (CDC) reports more than 480,000 deaths are caused by smoked tobacco annually in the United States,[3] and nearly 90,000 deaths are caused by excessive use of alcohol.[4]

Cannabis is Accepted in the Medical Community as a Safe and Effective Medication

24. Since the passage of the medical cannabis laws in states such as California, controlled studies have confirmed that cannabis is a safe and effective medicine for treating many medical conditions.

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[3] Center for Disease Control and Prevention: Tobacco Related Mortality 2014, States,http://www.cdc.gov/tobacco/data_statistics/fact_sheets/index.htm

[4] Center for Disease Control and Prevention: Fact Sheet Alcohol Use and Health, 2014 http://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm. Furthermore, the 2014 WHO (World Health Organization) Report on Alcohol-Induced Mortality found there were 3.3 million alcohol-related deaths in 2012 worldwide. http://www.who.int/substance_abuse/publications/global_alcohol_report/en/

25. Medical practitioners overwhelmingly support the use of cannabis as medicine. A survey conducted by the *New England Journal of Medicine* in 2013 found that the majority of clinicians polled in favor of the use of marijuana for the medical treatment of a 68-year-old woman with metastatic breast cancer in the alleviation of her symptoms, tallying 76% of the 1446 votes. Again, in April, 2014, a WebMD survey evidenced that 69% of surveyed physicians believed cannabis can help with certain treatments and conditions, and 67% agreed that cannabis should be a medical option for patients.[5]

26. Numerous associations of physicians and other medical practitioners in this country have called for the legalization of cannabis as medicine, including, but not limited to: the Epilepsy Foundation of America, American Medical Student Association, American Nurses Association, American Preventive Medical Association, American Public Health Association, as well as various associations for the following states: Alaska, California, Colorado, Connecticut, Florida, Hawaii, Illinois, Mississippi, New Jersey, New Mexico, New York, North Carolina, Rhode Island, Texas, Vermont, and Wisconsin. Further, many others, including but not limited to the American Medical Association and the American Cancer Society, have called for further clinical research into the potential medical benefits of cannabis.

27. Cannabis has also been increasingly recognized as an effective and safe medicine in government-funded studies.

28. For example, the National Institutes of Health's National Institute on Drug Abuse [NIDA] funded a project performed at the University of California at Los Angeles. The purpose of this project was to determine if smoking cannabis increased the risk of cancer similar to smoking tobacco. The researchers concluded: "[C]ontrary to our expectations, we found no positive associations between marijuana use and lung or UAT [Upper Aerodigestive Tract] cancers. Although we observed positive

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[5] http://www.webmd.com/news/breaking-news/marijuana-on-main-street/20140225/webmd-marijuana-survey-web

dose-response relations of marijuana use to oral and laryngeal cancers in the crude analyses, the trend was no longer observed when adjusting for potential confounders, especially cigarette smoking. In fact, we observed ORs <1 for all cancers except for oral cancer, and a consistent monotonic association was not apparent for any outcome."[6]

29. Beginning in 2000, the state of California sponsored a number of randomized, placebo controlled trials evaluating the safety and therapeutic efficacy of whole smoked cannabis for a variety of patient populations, including subjects diagnosed with multiple sclerosis, HIV, and chronic neuropathy. A review of these trials, published in 2012, by Igor Grant, M.D., (CMCR), J. Hampton Atkinson, Ben Gouaux, and Barth Wilse, concluded:

> Based on evidence currently available the Schedule I classification is not tenable; it is not accurate that cannabis has no medical value, or that information on safety is lacking. It is true cannabis has some abuse potential, but its profile more closely resembles drugs in Schedule III (where codeine and dronabinol are listed). The continuing conflict between scientific evidence and political ideology will hopefully be reconciled in a judicious manner.[7]

30. Even the National Highway Traffic Safety Administration, a Federal agency, has published reports recognizing the medicinal use of cannabis in its Drugs and Human Performance Fact Sheet, which states:

> Medical and Recreational Uses: Medicinal: Indicated for the treatment of anorexia associated with weight loss in patients with AIDS and to treat mild to moderate nausea and vomiting associated with cancer chemotherapy.

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[6] Hashibe et al. 2006. *Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study* 15: Cancer Epidemiology Biomarkers and Prevention: 1829

[7] Igor Grant, M.D., et. al., "*Medical Marijuana: Clearing Away the Smoke*," The Open Neurology Journal, 2012, 6, p. 18-25.

31. In my practice, I cautioned patients to avoid driving after using many prescription drugs, over the counter medications, as well as cannabis. I believe cannabis can influence psychomotor performance, particularly among more naive subjects and/or if consumed in concert with alcohol. The relative risk, however, associated with marijuana-only positive drivers and accidents is relatively low. Further, studies have shown that the impact of cannabis use on driving performance is far less than many over-the-counter medications. The federal government's own sponsored studies inform this opinion and, in fact, National Highway Traffic Administration (NHTSA) recently published the first large-scale case-control study ever conducted in the United States to assess the crash risk associated with both drugs and alcohol use by drivers, ultimately determining that drivers who test positive for the presence of THC in blood are *no* more likely to be involved in motor vehicle crashes than are drug-free drivers. *See*, NHTSA, Drug and Alcohol Crash Risk (February 2015), finding that THC-positive drivers' elevated risk of accident was zero (OR=1.05) after confounding for demographic variables such as age, gender, race and ethnicity.[8]

32. Further, in 2013, a meta-analysis published in the Journal *Accident Analysis and Prevention* indicates that the adjusted odds ratio for the likelihood of a marijuana positive driver being culpable in a traffic accident compared to a drug-negative driver is just above 1 (not statistically significant at the 5% level) and is on par with the odds ratios associated with penicillin and anti-histamines.[9] By contrast, a recent paper identified greater odds of culpability of accident associated with drivers with a BAC of .01% (OR=1.46).[10]

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[8] http://www.nhtsa.gov/About+NHTSA/Press+Releases/2015/nhtsa-releases-2-impaired-driving-studies-02-2015

[9] Rune Elvik. 2013. *Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies*. Accident Analysis and Prevention 60: 254-267.

[10] http://injuryprevention.bmj.com/content/early/2014/01/07/injuryprev-2013-040925.

33. Due to cannabis' status as a Schedule I substance, researchers desirous of obtaining marijuana for scientific and medical study must, by federal statute, seek approval from the DEA, Public Health Service, FDA, and the NIDA. While this has proven to be difficult for some investigators, clinical studies evaluating the safety and therapeutic efficacy of cannabis are being conducted both in the United States and abroad.[11] I have listed numerous peer-reviewed papers assessing the therapeutic use of cannabis in human subjects in the attached addendum; these include several randomized, placebo-controlled trial designs. This body of research demonstrates remarkable promise in using cannabis to treat the following illnesses, diseases and symptoms: Parkinson's Disease, Crohn's Disease, Pain, Epilepsy, Cancer, Irritable Bowl Syndrom, Diabetes, Post Traumatic Stress, Neuropathy, Multiple Sclerosis, HIV, Fibromyalgia, Cluster Headaches, Hepatitis C, and Incontinence. Additionally, a recent study demonstrated that a high CBD form of cannabis could be an effective treatment for schizophrenia.[12]

34. Further, research was presented at the Eighth National Clinical Conference on Cannabis Therapeutics (a Continuing Medical Education course) in 2014. Physicians and scientist from around the world presented the results of studies conducted to test the efficacy and danger of using cannabis to treat Alzheimer's Disease (Julian Romero, Ph.D.), Neuromuscular Diseases, (Greg Carter, M.D.), Hepatitis C, (Diana Silvestre, M.D.), Cancer, (Donald Abrams, M.D, and Sara Jane Ward, Ph.D.) Cardiovascular Problems (Reem Smoum, Ph.D.), Cannabis Use in Nursing Homes in

[11] It should be noted that Dr. Tashkin had some difficulty getting his research paper published after his results demonstrated cannabis was not a carcinogenic despite the fact that it was sponsored by the National Institutes of Health. Also, Donald Abrams, M.D., had difficulty acquiring research grade cannabis for his landmark study dealing with cannabis and AIDS. And, Dr Lyle Craker's attempts to acquire a license to produce research grade cannabis, like the one issued in Mississippi for the NIDA program, have been unsuccessful.

[12] http://www.ncbi.nlm.nih.gov/pubmed/25667194

both California and Israel (Jeffrey Hergenrather, M.D., and Zack Klein, MSc[13] Candidate), Cannabis Use in Hospice and Palliative Medicine, (Sunil Aggarwal, M.D. Ph.D.) These studies overwhelmingly conclude that cannabis is an effective and safe medicine. Further, these results are supported by the scientific understanding of how the naturally occurring endocannabinoids react and interact with various cannabinoids in the marijuana plant which explains the remarkable heath improvement.

35. Since the passage of the medical cannabis laws in states such as California, scientific studies have confirmed that cannabis is a safe and effective medicine for treating many medical conditions. In 2011, Gregory T. Carter, MD, MS, Mitchell Earleywine, PhD, and Jason T. McGill, JD, prepared a comprehensive report outlining the research and scientific evidence supporting the use of cannabis as medicine which was incorporated into a petition brought by several state Governors pressing for the rescheduling of marijuana. The report concludes that the mounting scientific evidence and consensus of medical opinion support the position I propose: it is irrational to classify marijuana as a Schedule I controlled substance as it fails to meet the criteria for so doing.

[13] The use of cannabis to treat patients suffering from dementia and Parkinson's Disease at a nursing home in Tel-Aviv was featured on a special television program reported by Sanja Gupta. (*See*, http://edition.cnn.com/TRANSCRIPTS/1403/09/se.01.html.) It included 27 patients, some of whom are Holocaust survivors, and demonstrate the following results after cannabis treatment: (1) Discontinuation of pain relief medications, (2) improvement of appetite and weight gain, (3) Improvement in eating ability, (4) decreased muscle contractions, (5) Improved sleep and decrease in the use of sleeping medications, and (6) discontinues use of enema treatments. Observational data from 113 cancer patients using cannabis at an academic medical center in Israel was published on June 14, 2014, and concluded: "Cannabis use is perceived as highly effective by some patients with advanced cancer and its administration can be regulated, even by local authorities. Additional studies are required in order to evaluate the efficacy of cannabis as part of the palliative treatment of cancer patients." J Pain Symptom Manage 2014 Jun 14, *Patterns of Use of Medical Cannabis Among Israeli Cancer Patients: A Single Institution Experience*. http://www.ncbi.nlm.nih.gov/pubmed/24937161.

Further, the report refutes all assertions recently made by the DEA regarding the harmful effects of cannabis.

36. Notably, the United States Surgeon General, or "the Nation's Doctor," is tasked generally with providing "Americans with the best scientific information available on how to improve their health and reduce the risk of illness and injury."[14] Our current Surgeon General, Dr. Vivek Murthy recently stated that "for certain medical conditions and symptoms, that marijuana can be helpful."[15]

Cannabis can be safely used particularly under medical supervision

37. The federal government has conducted its own medical cannabis program through the National Institutes of Drug Abuse which has been supervising the distribution of marijuana for medical purposes for almost forty years to patients, including Irvin Rosenfeld and numerous others.

38. As a physician practicing in California following the passage of the Compassionate Use Act, I was easily able to monitor my patients use of cannabis as medicine. In fact, because marijuana has minimal toxicity and has limited side effects, patients using cannabis are much easier to care for than those taking routinely prescribed medications.

39. Furthermore, as a founding member of The Society of Cannabis Clinicians as well as through my involvement in other professional organizations, I have had many opportunities to discuss the experiences of my colleagues who agree supervision of cannabis patients pose few

[14] http://www.surgeongeneral.gov/about/index.html.

[15] Located online at: http://www.cbsnews.com/news/surgeon-general-dr-vivek-murthy-on-measles-vaccine-marijuana-legalization/, documenting the videotaped interview with Dr. Vivek Murthy, Surgeon General of the United States. As such statements were videotaped and aired throughout the nation, the statements are both (1) generally known within the Eastern District and (2) its sources are readily determined from sources whose accuracy cannot reasonably be questioned. *See, FRE 201(b)(1), (2).*

medical concerns. In fact, the greatest concern for our medical cannabis patients arises out of the fact that marijuana remains illegal for all purposes under federal law, thereby increasing the price of obtaining their medicine and the risk of cultivating the plant.

40. The argument is sometimes made that the risks described above can be avoided since the medicinal benefits of marijuana are available through prescription Marinol - a synthetic form of THC approved by the FDA for the treatment of wasting syndrom associated with cancer and AIDS. Patients, however, report that the use of Marinol is ineffectual because swallowing a pill can prove impossible for those using the drug to reduce nausea. Moreover, Marinol incorporates only the one cannabanoid, ironically the one which produces the most psychoactive effect, yet studies have established that cannabidiol (CBD), a non-psychoactive cannabinoid, is effective in treating many serious illnesses including controlling seizures.

41. As is obvious from the studies referenced in my addendum, the therapeutic qualities of the cannabis plant reach far beyond the treatment of anorexia and nausea

42. In fact, while there has yet to be a clinical trial testing the hypothesis, there is much acceptance within the medical community regarding the potential benefits produced from strains of marijuana which contain low levels of THC. Just three weeks ago, GW Pharmaceuticals announced it had begun two Phase 3 trials of Epidiolex, which contains cannabidiol (CBD), one of the cannabinoids found in the marijuana plant which GW Pharmaceuticals derives from whole-plant cannabis, to determine its efficacy in the treatment of Lennox-Gastaut syndrome (LGS), a rare and severe form of childhood-onset epilepsy.[16] In hopes of submitting a New Drug Application for Epidiolex to the FDA in mid-2016, the company is also in the midst of two additional Phase 3 trials

[16] http://ir.gwpharm.com/releasedetail.cfm?ReleaseID=912152

of Epidiolex in the treatment of Dravet syndrome, rare and catastrophic treatment-resistant form of childhood epilepsy.[17] Prior to the initiation of these Phase 3 studies, GW Pharmaceuticals had released clinical data evaluating the use of Epidiolex in 27 patients with intractable pediatric epilepsy which indicated an overall reduction in seizure frequency as compared to baseline seizure frequency was 44% and median overall reduction in seizure frequency as compared to baseline seizure frequency was 42%.[18]

43. Since the publicity surrounding the use of a high CBD/low THC strain of the cannabis to treat a six year old child suffering from Dravet Syndrom in Colorado, families with children suffering from seizure disorders have been relocating to Colorado in order to seek cannabis treatment. Margaret Gedde, M.D., a Colorado Springs physician, has been monitoring 11 children using cannabis to treat their severe seizures. In a November 2013 interview with a reporter from the Salt Lake City Tribune, Dr. Gedde reported nine of these children have had a 90 to 100 percent reduction in their seizures, one has had a 50% reduction, and one has reported no change.

44. It is apparent that medical supervision is not only possible, but is occurring in places like Colorado where the community has come together to successfully supervise the administration of cannabis to the most vulnerable of our society: severely compromised young children.

45. The Diagnostic and Statistical Manual of Mental Disorders (DSM) (Fifth Ed.) establishes that diagnostic criteria for Cannabis Use Disorder are far less severe than nearly every other

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[17] http://www.gwpharm.com/GW%20Pharmaceuticals%20Initiates%20Second%20Phase%203%20Pivotal%20Trial%20for%20Epidiolex%20in%20Dravet%20Syndrome.aspx

[18] While the children in these studies are being treated with cannabis-based extract containing high concentrations of cannabidiol - a naturally occurring compound in cannabis, this extract is still classified as a Schedule I Controlled Substance in the United States.

substance use disorder described therein, providing: "[i]n cases for which multiple types of substances are used, many times the individual may minimize the symptoms related to cannabis, as the symptoms may be *less severe* or cause *less harm* than those directly related to the use of other substances." (DSM V, p. 511.) The criteria indicative of Cannabis Use Disorder are most similar to that of Caffeine Use Disorder; however, remarkably, the Functional Consequences of Caffeine Intoxication can be fatal; not so for cannabis.

46. Also of great significance is the distinction for disorders related to medications (pp. 487-490), as the DSM V recognizes "medication-induced mental disorders are seen with prescribed or over-the-counter medications that are taken at suggested doses." The effects of prescription and over-the-counter drugs described are far greater than those articulated in the same section for cannabis:

> Psychotic syndromes may be temporarily experienced in the context of anticholinergic, cardiovascular, and steroid drugs, as well as use of stimulant-like and depressant-like prescription or *over-the-counter drugs*. Temporary but severe mood disturbances can be observed with a wide range of medications, including steroids, antihypertensives, disulfrum, and any prescription or *over-the-counter* depressant or stimulant-like substances. A similar range of medications can be associated with temporary anxiety syndromes, sexual dysfunctions, and conditions of disturbed sleep." (p. 488.)

47. Importantly, the DSM V requires the medical use of cannabis be considered before making a cannabis use disorder diagnosis, as symptoms of tolerance and withdrawal will naturally occur when a substance is taken as indicated for a medical condition and should not be used as the primary criteria for determining a diagnosis of a substance use disorder. (p. 511-512.)

48. In sum, it is my considered opinion that including marijuana and THC in Schedule I of the Controlled Substances Act is inappropriate for the following reasons:

A. Medicinal cannabis is effective for many medical conditions;

B. Medicinal cannabis can be used safely, particularly under medical supervision;

C. Medicinal cannabis is safer than the use of many other commonly used medications;

D. The major harm of cannabis use is its continued illegality.

I declare under penalty of perjury that the foregoing is true and correct, except for those matters stated on information and belief, and as to those matters I believe them to be true. This declaration signed on the 1st day of June, 2015, in Pahoa, Hawaii.

/s/ Philip A. Denney, M.D.
PHILIP A. DENNEY, M.D.

DECLARATION OF PHILIP A DENNEY, M.D.
ADDENDUM

I, Philip A. Denney, M.D., provide the following as a non-exhaustive list of recent, relevant controlled trials, case-reports, observational trials, survey data, or reviews in the peer-reviewed literature indicating the safety and efficacy of the administration of whole-plant cannabis or cannabinoids in specific patient populations. I have distinguished for this Court these research papers as they are the most informative due to the applied scientific design of the study.

1. Waissengrin B et al. 2014 Jun 14 [Epub ahead of print] Patterns of Use of Medical Cannabis Among Israeli Cancer Patients: A Single Institution Experience. *Journal of Pain Symptom Management* (2014. Doi:10.1016/j.painsymman.2014.05.018. SURVEY AND OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

2. Lotan et al., 2014. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. Clinical Neuropharmacology 37: 41-44. OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

3. Natfali et al., 2013. Cannabis Induces a Clinical Response in Patients with Crohn's Disease: a Prospective Placebo-Controlled Study. Clinical Gastroenterology and Hepatology 11: 1276-1280. CLINICAL, PLACEBO-CONTROLLED

4. Cooper et al, 2013. Comparison of the Analgesic Effects of Dronabinol and Smoked Marijuana In Daily Marijuana Smokers. Neuropsychopharmacology 38: 1984-1992. CLINICAL, PLACEBO-CONTROLLED

5. Porter and Jacobson. 2013. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy & Behavior 29: 574-577 SURVEY

6. Singh and Bali. 2013. Cannabis extract treatment for terminal acute lymphoblastic leukemia with a Philadelphia chromosome mutation. Case reports in Oncology 6: 585-592. CASE SUMMARY

7. Ravikoff et al., 2013. Marijuana use patterns among patients with inflammatory bowel disease. Inflammatory Bowel Diseases 19: 2809-2814. SURVEY

8. Penner et al. 2013. Marijuana use on glucose, insulin, and insulin resistance among US adults. American Journal of Medicine 126: 583-589. OBSERVATIONAL, CASE-CONTROL

9. Grant et al., 2012. Medical marijuana: Clearing away the smoke. The Open Neurology Journal 6: 18-25. LITERATURE REVIEW

10. Bostwick. 2012. Blurred boundaries: The therapeutics and politics of medical marijuana. Mayo Clinic Proceedings 2: 172-186. LITERATURE REVIEW

11. Passie et al., 2012. Mitigation of post-traumatic stress symptoms by Cannabis resin: a review of the clinical and neurobiological evidence. Drug Testing & Analysis 4: 649-659. CASE SUMMARY

12. Rajavashisth et al. 2012. Decreased prevalence of diabetes in marijuana users. BMJ Open 2 OBSERVATIONAL, CASE-CONTROL

13. Wilsey et al., 2012. Low-dose vaporized cannabis significantly improves neuropathic pain. The Journal of Pain 14: 136-148. CLINICAL, PLACEBO CONTROLLED

14. Corey-Bloom et al. 2012. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. Journal of the Canadian Medical Association 184: 1143-50. CLINICAL, PLACEBO-CONTROLLED

15. Riggs et al.. 2011. A pilot study of the effects of cannabis on appetite hormones in HIV-infected adult men. Brain Research 1431: 46-52. CLINICAL, PLACEBO-CONTROLLED

16. Abrams et al. 2011. Cannabinoid-opiod interaction in chronic pain. Clinical Pharmacology & Therapeutics 90: 844-851. CLINICAL, OBSERVATIONAL (NO PLACEBO GROUP)

17. Fiz et al. 2011. Cannabis use in patients with fibromyalgia: Effect on symptoms relief and health-related quality of life. PLoS One 6. OBSERVATIONAL, CASE-CONTROL

18. Lal et al. 2011. Cannabis use among patients with inflammatory bowel disease. European Journal of Gastroenterology & Hepatology 23: 891-896. SURVEY

19. Naftali et al. 2011. Treatment of Crohn's disease with cannabis: an observational study. Journal of the Israeli Medical Association 13: 455-458. OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

20. Foroughi et al., 2011. Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas--possible role of Cannabis inhalation. Child's Nervous System 27: 671-679. CASE REPORT

21. Ware et al. 2010. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 182: 694-701. CLINICAL, PLACEBO-CONTROLLED

22. Hazekamp and Grotenhermen. 2010. Review on clinical studies with cannabis and cannabinoids 2005-2009. (Special issue): 1-21 LITERATURE REVIEW

23. Robbins et al. 2009. Cluster attacks responsive to recreational cannabis and dronabinol. Headache 49: 914-916 CASE REPORT

24. Corless et al. 2009. Marijuana effectiveness as an HIV self-care strategy. Clinical Nursing Research 18: 172-193. SURVEY

25. Costain. 2008. The effects of cannabis abuse on the symptoms of schizophrenia: patient perspectives. International Journal of Mental Health Nursing 17: 227-235. SURVEY

26. Wilsey et al. 2008. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. Journal of Pain 9: 506-521. CLINICAL, PLACEBO-CONTROLLED

27. Ellis et al. 2008. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 34: 672-80. CLINICAL, PLACEBO-CONTROLLED

28. Abrams et al. 2007. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 68: 515-521. CLINICAL, PLACEBO-CONTROLLED

29. Wallace et al. 2007. Dose-dependent Effects of Smoked Cannabis on Capsaicin-induced Pain and Hyperalgesia in Healthy Volunteers. Anesthesiology 107: 785-796. CLINICAL, PLACEBO-CONTROLLED

30. Haney et al. 2007. Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep. Journal of Acquired Immune Deficiency Syndrome 45: 545-554. CLINICAL, COMPARATIVE (NO PLACEBO GROUP)

31. Rog et al. 2007. Oromucosal delta-9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clinical Therapeutics 29: 2068-2079. OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

32. Sylvestre et al. 2006. Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. European Journal of Gastroenterology & Hepatology. 18: 1057-1063. OBSERVATIONAL, CLINICAL (NO PLACEBO)

33. Pacher et al. 2006. The endocannabinoid system as an emerging target for pharmacotherapy. Pharmacological Reviews 58: 389-462. LITERATURE REVIEW

34. Chong et al. 2006. Cannabis use in patients with multiple sclerosis. Multiple Sclerosis 12: 646-651. SURVEY

35. Wade et al. 2006. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms of multiple sclerosis. Multiple Sclerosis 12: 639-645. OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

36. Amar. 2006. Cannabinoids in medicine: A review of their therapeutic potential. Journal of Ethnopharmacology 105: 1-25 LITERATURE REVIEW

37. Woolridge et al. 2005. Cannabis use in HIV for pain and other medical symptoms. Journal of Pain and Symptom Management 29: 358-367. SURVEY

38. Rog et al. 2005. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 65: 812-819. CLINICAL, PLACEBO-CONTROLLED

39. Gorter et al. 2005. Medical use of cannabis in the Netherlands. *Neurology* 64: 917-919. SURVEY

40. Swift et al. 2005. Survey of Australians using cannabis for medical purposes. *Harm Reduction Journal* 4: 2-18. SURVEY

41. Ware et al. 2005. The medicinal use of cannabis in the UK: results of a nationwide survey. *International Journal of Clinical Practice* 59: 291-295. SURVEY

42. Brady et al. 2004. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Multiple Sclerosis 10: 425-433. CLINICAL, OBSERVATIONAL (NO PLACEBO GROUP) LITERATURE REVIEW

43. Venderova et al. 2004. Survey on cannabis use in Parkinson's disease: subjective improvement of motor symptoms. Movement Disorders 19: 1102-1106. SURVEY

44. Gross et al., 2004. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center. Neurology 62: 2095-2097. SURVEY

45. Abrams et al. 2003. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. Annals of Internal Medicine 139: 258-266. CLINICAL, PLACEBO-CONTROLLED

46. Russo et al. 2002. Chronic cannabis use in the Compassionate Investigational New Drug program: An examination of benefits and adverse effects of legal clinical cannabis. Journal of Cannabis Therapeutics 2: 3-57. CLINICAL, OBSERVATIONAL (NO PLACEBO GROUP).

47. Wallace, Mark et al. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. Journal of Pain. 2015, Apr 3. [Epub ahead of print.] RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED CROSSOVER STUDY

48. Alshaarawy, Omayma, et al. Cannabis Smoking and Diabetes Mellitus. Results from Meta-analysis with Eight Independent Replication Samples. Epidemiology. [Epub ahead of print.] SURVEY

49. Thomas, Anil A., et al. Association Between Cannabis Use and the Risk of Bladder Cancer: Results From the California Men's Health Study. Oncology. 2015 Feb;85(2):388-92. SURVEY

50. Iseger, Tabitha A. et al. A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia Research*. 2015 Mar;162(1-3):153-61. META-ANALYSIS

51. Lau, Nicholas et al. A safer alternative: Cannabis substitution as harm reduction. *Drug and Alcohol Review*. (2015.) 2015 Apr 28. [Epub ahead of print.] SURVEY

52. Finseth et al. Self reported efficacy of cannabis and other complementary medicine modalities by Parkinson's disease patients in Colorado. Evidence-Based Complementary and Alternative Medicine. 2015;2015:874849. SURVEY

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EXHIBIT 1

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CURRICULUM VITAE

PERSONAL:

Age 55; Married to Latitia; Three children: Sarah, age 29, Elizabeth, age 27, Camille 19; Height 5'10"; Weight 180 lbs.

BACKGROUND:

Born in Washington, D.C.; raised in Hyattsville, MD. Father – Architect; Mother – Registered Nurse. Eldest of three brothers and four sisters. Roman Catholic primary and high school education with participation in baseball, football and boxing with Hyattsville Boys Club.

MILITARY:

U. S. Navy (1966-1972); Active Duty (1966-1970). Aircraft Emergency Equipmentman Second Class (ES), Antisubmarine Flight Crewman, Atlantic Patrol, 1,000 hours flight time. Sport parachute team member.

EDUCATION:

- Pennsylvania State University (1968)
- Bucks County Community College (1968-1971)
- Ohio University (1970-1972); Honors College (1971)
  - Board of Directors of United Campus Ministry (1971)
  - Psychiatric Technician, Athens State Hospital (1970-1972)
  - Clavine Alkaloid Research (1972)
- University of Southern California School of Medicine (1972-1976)
  - Doctor of Medicine (June 3, 1976)
  - Foothill Free Clinic (1974-1976)
  - CMA Alternate Delegate (1973-1974); CMA Delegate (1974-1975)
  - Consultant Reference Committee "B" CMA (1975)

PROFESSIONAL ACTIVITIES:

- L.A. County – USC Medical Center – Flex "A" rotating internship (1976-1977)
- Auburn Medical Clinic, Auburn, CA – Group general and family medical practice (1977-1978)
- Greenwood Medical Clinic, Greenwood, CA – Solo general and family medical practice (1978-1984)
- Sacramento Emergency Medical Group, Cordova Health Center, Rancho Cordova, CA – Urgent Care/Family practice (1984-1987)
- Med Center Medical Group, Citrus Heights, CA – Facility Medical Director, Urgent Care/Family practice (1987-1989)
- Sierra Pacific Emergency Medical Group, Mercy San Juan Hospital Satellite Facility, Carmichael, CA – Assistant Medical Director/Emergency Services (1989-1994)
- Medical Clinic of Sacramento, Sacramento, CA – Urgent Care (1994-1996)
- Meridian Occupational Medicine Group, Sacramento, CA – Facility Medical Director (1996-1997)
- Healthsouth Medical Clinic, Rocklin, CA – Facility Medical Director (1997-1999)
- Marshall Hospital – Medical Director, Marshall Center for Occupational Health (1999-2000)
- Philip A. Denney, M D – Medical Cannabis Evaluation (2000- Present)
- Medicinal Cannabis Testimony – Alameda, Alpine, Butte, El Dorado, Humboldt, Napa, Nevada, Placer, Riverside, Sacramento, San Bernardino, San Francisco, San Joaquin, Santa Clara, Shasta, Sonoma, Stanislaus, Tehama, Trinity and Tulare Counties
- Guest lecturer- USC School of Medicine- Clinical Uses of Cannabis (2005)
- Testimony Medicinal Cannabis Policy- Arkansas State Legislature (2005)

HOSPITAL PRIVILEGES:

- Auburn Faith Community Hospital – Attending staff in family medicine, pediatrics and obstetrics (1977-1985)
- Sutter General Hospital – Attending staff, family practice (1985-1987)
- Mercy San Juan Hospital – Senior staff, emergency medicine (1989-1994)
- Marshall Hospital-Courtesy staff (1999 to 2000)
- California License G34393; BNDD Number AD 7581045

PROFESSIONAL SOCIETIES:

- Society of Cannabis Clinicians- President (2006 to present)

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF IOWA
DAVENPORT DIVISION

UNITED STATES OF AMERICA, Plaintiff, vs. AEDAN MACDONALD, *et al.* Defendants.	No. 3:14-cr-53 **DECLARATION OF PHILIP A. DENNEY, M.D. IN SUPPORT OF DEFENDANT'S MOTION TO DISMISS**

I, PHILIP A. DENNEY, M.D. declare as follows:

I am a retired physician who was first licensed to practice medicine in the State of California in 1977. I attended medical school at the University of Southern California after serving in the United States Navy. Since graduation I have practiced Family, Emergency and Occupational Medicine. I have never been disciplined by the Medical Board, nor have my hospital privileges been revoked, suspended or restricted. I have been involved in the emerging field of cannabis medicine since 1999, and have practiced in Loomis, Redding, Lake Forrest, Oakland and Sacramento, California. I retired from active practice in 2010, but have continued to study the developments in medical cannabis scientific/medical research.

I have qualified to testify as an expert witness regarding the medical use of cannabis in at least 21 counties throughout California as well as in the District Court for the Eastern District of California. I have also testified before the California Medical Board regarding medicinal cannabis. I am a founding member of the Society of Cannabis Clinicians, and have been active in the development of policy regarding cannabis as medicine in El Dorado County, and in this regard have been asked to consult with Judges, District Attorneys, and law enforcement officers about the medical use of cannabis. I also

testified before the Arkansas State Legislature regarding the implementation of cannabis as medicine laws and policies, and have been consulted by members of the campaign to legalize the medical use of cannabis in the state of Montana.

While cannabis is considered a Schedule I Controlled Substance under the federal law, the overwhelming majority of current medical research contradicts such a classification. A Schedule I "Controlled Substance" is defined in *21 U.S.C. section 812(b)(1)* as follows:

(A) The drug or other substance has a high potential for abuse;

(B) The drug or other substance has no currently accepted medical use in treatment in the United States;

© There is a lack of accepted safety for use of the drug or other substance under medical supervision.

For the reasons provided in this declaration, and those which may be presented at hearing, it is my professional medical opinion that cannabis has a low potential for abuse, is currently accepted and used medically to treat multiple serious medical conditions, and has been safely used under medical supervision for nearly sixteen years in the State of California and elsewhere. Moreover, the safety and medical efficacy of cannabis far exceeds that of many other prescribed and over-the-counter (OTC) medications, in that it is less toxic, possesses a low abuse potential, and is incapable of causing lethal overdose.

Based on my training, experience, and review of pertinent human-subject clinical trials and other research conducted in accord with accepted principles and methodologies,[1] I have formed the opinion that cannabis fails to meet the criteria for inclusion in Schedule I of the Controlled Substances Act.

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[1] Attached hereto, and incorporated by reference, is an Addendum which highlights studies which I believe are of great significance to the issue before this Court, and therefore, exclude pre-clinical trials, animal studies and anecdotal evidence.

I attest to the following in support of this opinion:

Cannabis and Potential for Abuse

1. In determining whether a substance has a high potential for abuse, a physician assesses both the physical and psychological effect of the drug. It is my opinion that cannabis has minimal potential for physical abuse, and low potential for psychological abuse.

2. Cannabis is a non-toxic, non-lethal substance. There have been *no* confirmed deaths resulting from an overdose of marijuana and, in fact, based on the physiological properties of the plant, an overdose would be, as a practical matter, impossible.

3. Many over-the-counter medications pose inherent health risks, and some are toxic even when used as recommended. As detailed, *infra*, adverse effects and/or overdoses can result in permanent major organ failure and death.

4. Unlike many drugs, including some over-the-counter (OTC) medications, cannabis has a notably low abuse potential, and cessation causes minimal physiological symptoms of withdrawal.

5. While some studies have identified an association between cannabis use and psychosis, none have identified a causal relationship between cannabis use and mental illness in otherwise healthy individuals not already predisposed to these conditions. The association between marijuana use and mental illness is most likely not one of causation, but rather reflects the tendency of those in psychological distress to self-medicate, and the fact that diseases such as schizophrenia and bipolar disorder generally manifest themselves in late adolescents and early adulthood, which is the same age during which individuals are most likely to use illegal drugs. Further, the hypothesis that marijuana may cause the onset of these serious mental illnesses is contradicted by the evidence that worldwide rates of schizophrenia have largely remained static despite dramatically changing rates of cannabis use by various populations over multiple generations. In fact, through my training and experience I have found

cannabis has been successfully used to treat psychological disorders such as anxiety, depression and PTSD in a number of patients who have not found other treatments sufficiently helpful.

6. The psychological effects of cannabis are similar to those of many OTCs. For instance, relaxation, euphoria, and sedation are frequently reported with use of THC (the psychoactive cannabinoid in marijuana). These same symptoms are common with cough medicines, antihistamines, nausea medication, and many others.

7. Clinical trials and case studies on human subjects support my opinion that cannabis is not only an effective medicine, but one with fewer and less serious side effects than many medications in common use. Examples discussed in detail herein include:

A. Acetaminophen (OTC analgesics Tylenol)

B. Dextromethorphan: (OTC cough medications)

C. Acetylsalicylic Acid (aspirin)

D. Ibuprofen (Advil and Motrin)

A. Acetaminophen: Common Brand Name, Tylenol

8. Acetaminophen, is a widely used temporary pain reliever and fever reducer. The substance carries a warning of the potential for severe liver damage even at relatively low doses. For instance, the Physician's Desk Reference (PDR) for Nonprescription Drugs warns that sever liver damage may occur if a patient takes more than 6 650 mg caplets in a 24 hour period, yet the recommended dose for adults is 2 650 mg caplets every 8 hours. Accordingly even small amounts over the recommended dose could cause serious harm.

9. Other side effects of this substance include upper gastrointestinal complications such as bleeding, and kidney damage. There is also some evidence that chronic users of acetaminophen may

have a higher risk of developing blood cancer. For even modest users of alcohol, these effects are more pronounced.

10. The FDA issued a warning on August 2, 2013, that this substance could cause a serious skin reaction which could be fatal. Additionally, a 2010 study suggests that infertility of adults whose mother used acetaminophen while pregnant could be the result of such use.

11. Significantly, acetaminophen hepatotoxicity is the most common cause of acute liver failure in the United States, and results in more calls to poison control centers than the overdose of *any* other pharmacological substance. Even if treated, an overdose can lead to liver failure within days. While the most important toxic effect of acetaminophen is hepatic necrosis leading to liver failure after an overdose, there are also reported cases of renal failure after overdose. On January 14, 2014, the FDA issued a recommendation to health care professionals to discontinue prescription combination drug products with more than 325 mg of acetaminophen in order to protect consumers from liver damage. In April of 2014, the FDA had to "remind" health care professionals to stop dispensing prescription combination drug products with more than 325 mg of acetaminophen because they were "no longer considered safe by the FDA."

B. Dextromethorphan Common brand names: Benylin, Nyquil and Robitussin

12. Dextromethorphan, also referred to as DXM or DM, is used to temporarily relieve cough due to minor throat and bronchial irritation. DXM is widely abused as it acts as a dissociative hallucinogen. Even at recommended doses it can cause nausea, drowsiness, dizziness, difficulty breathing, skin rashes, and hallucinations. At higher doses DXM can result in hallucinations, dissociation, vomiting, hypotenstion, hypertension, tachycardia, diarrhea, muscle spasms, sedation, euphoria, black outs, and loss of sight.

13. In addition, DXM can have serious heath consequences when taken at the same time or shortly after taking certain prescription medication used to treat depression, psychiatric conditions, and Parkinson's Disease.

14. Because this product simulates the effects of alcohol, it may be subject to abuse and addiction in the same way, and has resulted in overdose.

C. Acetylsalicylic Acid

15. Acetylsalicylic Acid, or aspirin, is a nonsteroidal anti-inflammatory drug used to temporarily relieve minor aches and pains, and to reduce fever. Even recommended doses commonly cause Dyspepsia and mild to life-threatening gastrointestinal blood loss, and allergic reactions such as hives, shock, facial swelling and asthma. Reye's syndrome, which is a rare but commonly fatal childhood illness, is a known risk to the use of aspirin. Further, toxic doses of this substance can cause tinnitus, deafness, nausea, abdominal pain, flushing and fever.

D. Ibuprofen: Common brand names include Advil and Motrin.

16. Ibuprofen is a nonsteroidal anti-inflammatory used for temporary pain relief and fever reduction. It is common for those taking therapeutic doses to suffer nausea, dyspepsia, gastrointestinal ulcerations and bleeding, raised liver enzymes, diarrhea, constipation, epistaxis, headache, dizziness, rash, salt and fluid retention, and hypertension.

17. Ibuprofen may cause a severe allergic reaction, causing hives, facial swelling, asthma, shock, skin reddening, rash and blisters. Some studies indicate that chronic use of Ibuprofen may cause hypertension and possibly myocardial infarction, renal impairment, broncho spasm, and esophageal ulceration. Significantly, it can also be fatal to some asthmatics.

18. Also, when combined with diphenhydramine, the ingredients in Motrin PM, a patient is warned not to operate a motor vehicle, as it will cause drowsiness.

* * *

19. Cannabis has not been linked to any of the serious side-effects associated with the above described OTC medications.

20. A widely used measure of a drug's harmful effect is the Therapeutic Index, or Ratio. This refers to the relationship between toxic and therapeutic dose, and is calculated by determining the ratio of the dose that produces toxicity (TD50) and dividing it by that which produces a clinically desired or effective response (ED50), in 50% of the subjects. A low therapeutic index heightens the drug's potential to be lethal. Some over-the-counter medications have a low Therapeutic Index, meaning the difference between the therapeutic and toxic dose is very small. For example, the estimated Therapeutic Index for acetaminophen is less than 3 and may be lower with alcohol use. The Therapeutic Index for aspirin is less than 5 and bleeding can occur even at the recommended dose. In contrast, the Therapeutic Index for cannabis is estimated to be between 1,000 and 40,000.[2]

21. The following table compares the Therapeutic Index of above OTCs with cannabis:

Substance	**Therapeutic Index**
Cannabis	1000 - 40,000
Dextromethorphan: (cough meds)	< 10
Acetaminophen	< 3
Aspirin	< 5
Ibuprofen	< 20

[2] It should be noted that, since there are no confirmed deaths nor life threatening harm caused by the overdose of marijuana, the Therapeutic Index for cannabis is theoretical. Also, because it would be impossible to ingest 1,000 to 40,000 times the therapeutic dose within the time required to test its impact, practically the Therapeutic Index in the case of marijuana ingestion does not exist.

22. I have chosen to make the comparison between cannabis and over-the-counter medications to demonstrate the benign nature of the former; however, the obvious should be noted: the potential for abuse associated with prescription medications is far greater than that posed by OTCs, let alone cannabis. A comparison between cannabis and prescription medications demonstrates compelling evidence that the former is safer and can be more effective in treating illnesses. For example, the Therapeutic Index for many prescription medications such as psychiatric medications, opiates, cardiac medications, etc., are less than 10. The mortality rate for each of many prescription medications is significant. Furthermore, known side effects of prescription medications are far to numerous to here articulate. I can think of no prescription medication which has fewer potential harmful side effects than cannabis.

23. Finally, an evaluation of cannabis is not complete without comparing it to alcohol and tobacco. Tobacco being the more toxic substance, and alcohol a close second. The excess death rate associated with use and abuse of these substances is staggering. The Center for Disease Control and Prevention (CDC) reports more than 480,000 deaths are caused by smoked tobacco annually in the United States,[3] and nearly 90,000 deaths are caused by excessive use of alcohol.[4]

Cannabis is Accepted in the Medical Community as a Safe and Effective Medication

24. Since the passage of the medical cannabis laws in states such as California, controlled studies have confirmed that cannabis is a safe and effective medicine for treating many medical conditions.

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[3] Center for Disease Control and Prevention: Tobacco Related Mortality 2014, States,http://www.cdc.gov/tobacco/data_statistics/fact_sheets/index.htm

[4] Center for Disease Control and Prevention: Fact Sheet Alcohol Use and Health, 2014 http://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm. Furthermore, the 2014 WHO (World Health Organization) Report on Alcohol-Induced Mortality found there were 3.3 million alcohol-related deaths in 2012 worldwide. http://www.who.int/substance_abuse/publications/global_alcohol_report/en/

25. Medical practitioners overwhelmingly support the use of cannabis as medicine. A survey conducted by the *New England Journal of Medicine* in 2013 found that the majority of clinicians polled in favor of the use of marijuana for the medical treatment of a 68-year-old woman with metastatic breast cancer in the alleviation of her symptoms, tallying 76% of the 1446 votes. Again, in April, 2014, a WebMD survey evidenced that 69% of surveyed physicians believed cannabis can help with certain treatments and conditions, and 67% agreed that cannabis should be a medical option for patients.[5]

26. Numerous associations of physicians and other medical practitioners in this country have called for the legalization of cannabis as medicine, including, but not limited to: the Epilepsy Foundation of America, American Medical Student Association, American Nurses Association, American Preventive Medical Association, American Public Health Association, as well as various associations for the following states: Alaska, California, Colorado, Connecticut, Florida, Hawaii, Illinois, Mississippi, New Jersey, New Mexico, New York, North Carolina, Rhode Island, Texas, Vermont, and Wisconsin. Further, many others, including but not limited to the American Medical Association and the American Cancer Society, have called for further clinical research into the potential medical benefits of cannabis.

27. Cannabis has also been increasingly recognized as an effective and safe medicine in government-funded studies.

28. For example, the National Institutes of Health's National Institute on Drug Abuse [NIDA] funded a project performed at the University of California at Los Angeles. The purpose of this project was to determine if smoking cannabis increased the risk of cancer similar to smoking tobacco. The researchers concluded: "[C]ontrary to our expectations, we found no positive associations between marijuana use and lung or UAT [Upper Aerodigestive Tract] cancers. Although we observed positive

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[5] http://www.webmd.com/news/breaking-news/marijuana-on-main-street/20140225/webmd-marijuana-survey-web

dose-response relations of marijuana use to oral and laryngeal cancers in the crude analyses, the trend was no longer observed when adjusting for potential confounders, especially cigarette smoking. In fact, we observed ORs <1 for all cancers except for oral cancer, and a consistent monotonic association was not apparent for any outcome."[6]

29. Beginning in 2000, the state of California sponsored a number of randomized, placebo controlled trials evaluating the safety and therapeutic efficacy of whole smoked cannabis for a variety of patient populations, including subjects diagnosed with multiple sclerosis, HIV, and chronic neuropathy. A review of these trials, published in 2012, by Igor Grant, M.D., (CMCR), J. Hampton Atkinson, Ben Gouaux, and Barth Wilse, concluded:

> Based on evidence currently available the Schedule I classification is not tenable; it is not accurate that cannabis has no medical value, or that information on safety is lacking. It is true cannabis has some abuse potential, but its profile more closely resembles drugs in Schedule III (where codeine and dronabinol are listed). The continuing conflict between scientific evidence and political ideology will hopefully be reconciled in a judicious manner.[7]

30. Even the National Highway Traffic Safety Administration, a Federal agency, has published reports recognizing the medicinal use of cannabis in its Drugs and Human Performance Fact Sheet, which states:

> Medical and Recreational Uses: Medicinal: Indicated for the treatment of anorexia associated with weight loss in patients with AIDS and to treat mild to moderate nausea and vomiting associated with cancer chemotherapy.

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[6] Hashibe et al. 2006. *Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study* 15: Cancer Epidemiology Biomarkers and Prevention: 1829

[7] Igor Grant, M.D., et. al., "*Medical Marijuana: Clearing Away the Smoke*," The Open Neurology Journal, 2012, 6, p. 18-25.

31. In my practice, I cautioned patients to avoid driving after using many prescription drugs, over the counter medications, as well as cannabis. I believe cannabis can influence psychomotor performance, particularly among more naive subjects and/or if consumed in concert with alcohol. The relative risk, however, associated with marijuana-only positive drivers and accidents is relatively low. Further, studies have shown that the impact of cannabis use on driving performance is far less than many over-the-counter medications. The federal government's own sponsored studies inform this opinion and, in fact, National Highway Traffic Administration (NHTSA) recently published the first large-scale case-control study ever conducted in the United States to assess the crash risk associated with both drugs and alcohol use by drivers, ultimately determining that drivers who test positive for the presence of THC in blood are *no* more likely to be involved in motor vehicle crashes than are drug-free drivers. *See*, NHTSA, Drug and Alcohol Crash Risk (February 2015), finding that THC-positive drivers' elevated risk of accident was zero (OR=1.05) after confounding for demographic variables such as age, gender, race and ethnicity.[8]

32. Further, in 2013, a meta-analysis published in the Journal *Accident Analysis and Prevention* indicates that the adjusted odds ratio for the likelihood of a marijuana positive driver being culpable in a traffic accident compared to a drug-negative driver is just above 1 (not statistically significant at the 5% level) and is on par with the odds ratios associated with penicillin and anti-histamines.[9] By contrast, a recent paper identified greater odds of culpability of accident associated with drivers with a BAC of .01% (OR=1.46).[10]

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[8] http://www.nhtsa.gov/About+NHTSA/Press+Releases/2015/nhtsa-releases-2-impaired-driving-studies-02-2015

[9] Rune Elvik. 2013. *Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies*. Accident Analysis and Prevention 60: 254-267.

[10] http://injuryprevention.bmj.com/content/early/2014/01/07/injuryprev-2013-040925.

33. Due to cannabis' status as a Schedule I substance, researchers desirous of obtaining marijuana for scientific and medical study must, by federal statute, seek approval from the DEA, Public Health Service, FDA, and the NIDA. While this has proven to be difficult for some investigators, clinical studies evaluating the safety and therapeutic efficacy of cannabis are being conducted both in the United States and abroad.[11] I have listed numerous peer-reviewed papers assessing the therapeutic use of cannabis in human subjects in the attached addendum; these include several randomized, placebo-controlled trial designs. This body of research demonstrates remarkable promise in using cannabis to treat the following illnesses, diseases and symptoms: Parkinson's Disease, Crohn's Disease, Pain, Epilepsy, Cancer, Irritable Bowl Syndrom, Diabetes, Post Traumatic Stress, Neuropathy, Multiple Sclerosis, HIV, Fibromyalgia, Cluster Headaches, Hepatitis C, and Incontinence. Additionally, a recent study demonstrated that a high CBD form of cannabis could be an effective treatment for schizophrenia.[12]

34. Further, research was presented at the Eighth National Clinical Conference on Cannabis Therapeutics (a Continuing Medical Education course) in 2014. Physicians and scientist from around the world presented the results of studies conducted to test the efficacy and danger of using cannabis to treat Alzheimer's Disease (Julian Romero, Ph.D.), Neuromuscular Diseases, (Greg Carter, M.D.), Hepatitis C, (Diana Silvestre, M.D.), Cancer, (Donald Abrams, M.D, and Sara Jane Ward, Ph.D.) Cardiovascular Problems (Reem Smoum, Ph.D.), Cannabis Use in Nursing Homes in

[11] It should be noted that Dr. Tashkin had some difficulty getting his research paper published after his results demonstrated cannabis was not a carcinogenic despite the fact that it was sponsored by the National Institutes of Health. Also, Donald Abrams, M.D., had difficulty acquiring research grade cannabis for his landmark study dealing with cannabis and AIDS. And, Dr Lyle Craker's attempts to acquire a license to produce research grade cannabis, like the one issued in Mississippi for the NIDA program, have been unsuccessful.

[12] http://www.ncbi.nlm.nih.gov/pubmed/25667194

both California and Israel (Jeffrey Hergenrather, M.D., and Zack Klein, MSc[13] Candidate), Cannabis Use in Hospice and Palliative Medicine, (Sunil Aggarwal, M.D. Ph.D.) These studies overwhelmingly conclude that cannabis is an effective and safe medicine. Further, these results are supported by the scientific understanding of how the naturally occurring endocannabinoids react and interact with various cannabinoids in the marijuana plant which explains the remarkable heath improvement.

35. Since the passage of the medical cannabis laws in states such as California, scientific studies have confirmed that cannabis is a safe and effective medicine for treating many medical conditions. In 2011, Gregory T. Carter, MD, MS, Mitchell Earleywine, PhD, and Jason T. McGill, JD, prepared a comprehensive report outlining the research and scientific evidence supporting the use of cannabis as medicine which was incorporated into a petition brought by several state Governors pressing for the rescheduling of marijuana. The report concludes that the mounting scientific evidence and consensus of medical opinion support the position I propose: it is irrational to classify marijuana as a Schedule I controlled substance as it fails to meet the criteria for so doing.

[13] The use of cannabis to treat patients suffering from dementia and Parkinson's Disease at a nursing home in Tel-Aviv was featured on a special television program reported by Sanja Gupta. (*See*, http://edition.cnn.com/TRANSCRIPTS/1403/09/se.01.html.) It included 27 patients, some of whom are Holocaust survivors, and demonstrate the following results after cannabis treatment: (1) Discontinuation of pain relief medications, (2) improvement of appetite and weight gain, (3) Improvement in eating ability, (4) decreased muscle contractions, (5) Improved sleep and decrease in the use of sleeping medications, and (6) discontinues use of enema treatments. Observational data from 113 cancer patients using cannabis at an academic medical center in Israel was published on June 14, 2014, and concluded: "Cannabis use is perceived as highly effective by some patients with advanced cancer and its administration can be regulated, even by local authorities. Additional studies are required in order to evaluate the efficacy of cannabis as part of the palliative treatment of cancer patients." J Pain Symptom Manage 2014 Jun 14, *Patterns of Use of Medical Cannabis Among Israeli Cancer Patients: A Single Institution Experience*. http://www.ncbi.nlm.nih.gov/pubmed/24937161.

Further, the report refutes all assertions recently made by the DEA regarding the harmful effects of cannabis.

36. Notably, the United States Surgeon General, or "the Nation's Doctor," is tasked generally with providing "Americans with the best scientific information available on how to improve their health and reduce the risk of illness and injury."[14] Our current Surgeon General, Dr. Vivek Murthy recently stated that "for certain medical conditions and symptoms, that marijuana can be helpful."[15]

Cannabis can be safely used particularly under medical supervision

37. The federal government has conducted its own medical cannabis program through the National Institutes of Drug Abuse which has been supervising the distribution of marijuana for medical purposes for almost forty years to patients, including Irvin Rosenfeld and numerous others.

38. As a physician practicing in California following the passage of the Compassionate Use Act, I was easily able to monitor my patients use of cannabis as medicine. In fact, because marijuana has minimal toxicity and has limited side effects, patients using cannabis are much easier to care for than those taking routinely prescribed medications.

39. Furthermore, as a founding member of The Society of Cannabis Clinicians as well as through my involvement in other professional organizations, I have had many opportunities to discuss the experiences of my colleagues who agree supervision of cannabis patients pose few

[14] http://www.surgeongeneral.gov/about/index.html.

[15] Located online at: http://www.cbsnews.com/news/surgeon-general-dr-vivek-murthy-on-measles-vaccine-marijuana-legalization/, documenting the videotaped interview with Dr. Vivek Murthy, Surgeon General of the United States. As such statements were videotaped and aired throughout the nation, the statements are both (1) generally known within the Eastern District and (2) its sources are readily determined from sources whose accuracy cannot reasonably be questioned. *See, FRE 201(b)(1), (2).*

medical concerns. In fact, the greatest concern for our medical cannabis patients arises out of the fact that marijuana remains illegal for all purposes under federal law, thereby increasing the price of obtaining their medicine and the risk of cultivating the plant.

40. The argument is sometimes made that the risks described above can be avoided since the medicinal benefits of marijuana are available through prescription Marinol - a synthetic form of THC approved by the FDA for the treatment of wasting syndrom associated with cancer and AIDS. Patients, however, report that the use of Marinol is ineffectual because swallowing a pill can prove impossible for those using the drug to reduce nausea. Moreover, Marinol incorporates only the one cannabanoid, ironically the one which produces the most psychoactive effect, yet studies have established that cannabidiol (CBD), a non-psychoactive cannabinoid, is effective in treating many serious illnesses including controlling seizures.

41. As is obvious from the studies referenced in my addendum, the therapeutic qualities of the cannabis plant reach far beyond the treatment of anorexia and nausea

42. In fact, while there has yet to be a clinical trial testing the hypothesis, there is much acceptance within the medical community regarding the potential benefits produced from strains of marijuana which contain low levels of THC. Just three weeks ago, GW Pharmaceuticals announced it had begun two Phase 3 trials of Epidiolex, which contains cannabidiol (CBD), one of the cannabinoids found in the marijuana plant which GW Pharmaceuticals derives from whole-plant cannabis, to determine its efficacy in the treatment of Lennox-Gastaut syndrome (LGS), a rare and severe form of childhood-onset epilepsy.[16] In hopes of submitting a New Drug Application for Epidiolex to the FDA in mid-2016, the company is also in the midst of two additional Phase 3 trials

[16] http://ir.gwpharm.com/releasedetail.cfm?ReleaseID=912152

of Epidiolex in the treatment of Dravet syndrome, rare and catastrophic treatment-resistant form of childhood epilepsy.[17] Prior to the initiation of these Phase 3 studies, GW Pharmaceuticals had released clinical data evaluating the use of Epidiolex in 27 patients with intractable pediatric epilepsy which indicated an overall reduction in seizure frequency as compared to baseline seizure frequency was 44% and median overall reduction in seizure frequency as compared to baseline seizure frequency was 42%.[18]

43. Since the publicity surrounding the use of a high CBD/low THC strain of the cannabis to treat a six year old child suffering from Dravet Syndrom in Colorado, families with children suffering from seizure disorders have been relocating to Colorado in order to seek cannabis treatment. Margaret Gedde, M.D., a Colorado Springs physician, has been monitoring 11 children using cannabis to treat their severe seizures. In a November 2013 interview with a reporter from the Salt Lake City Tribune, Dr. Gedde reported nine of these children have had a 90 to 100 percent reduction in their seizures, one has had a 50% reduction, and one has reported no change.

44. It is apparent that medical supervision is not only possible, but is occurring in places like Colorado where the community has come together to successfully supervise the administration of cannabis to the most vulnerable of our society: severely compromised young children.

45. The Diagnostic and Statistical Manual of Mental Disorders (DSM) (Fifth Ed.) establishes that diagnostic criteria for Cannabis Use Disorder are far less severe than nearly every other

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[17] http://www.gwpharm.com/GW%20Pharmaceuticals%20Initiates%20Second%20Phase%203%20Pivotal%20Trial%20for%20Epidiolex%20in%20Dravet%20Syndrome.aspx

[18] While the children in these studies are being treated with cannabis-based extract containing high concentrations of cannabidiol - a naturally occurring compound in cannabis, this extract is still classified as a Schedule I Controlled Substance in the United States.

substance use disorder described therein, providing: "[i]n cases for which multiple types of substances are used, many times the individual may minimize the symptoms related to cannabis, as the symptoms may be *less severe* or cause *less harm* than those directly related to the use of other substances." (DSM V, p. 511.) The criteria indicative of Cannabis Use Disorder are most similar to that of Caffeine Use Disorder; however, remarkably, the Functional Consequences of Caffeine Intoxication can be fatal; not so for cannabis.

46. Also of great significance is the distinction for disorders related to medications (pp. 487-490), as the DSM V recognizes "medication-induced mental disorders are seen with prescribed or over-the-counter medications that are taken at suggested doses." The effects of prescription and over-the-counter drugs described are far greater than those articulated in the same section for cannabis:

> Psychotic syndromes may be temporarily experienced in the context of anticholinergic, cardiovascular, and steroid drugs, as well as use of stimulant-like and depressant-like prescription or *over-the-counter drugs*. Temporary but severe mood disturbances can be observed with a wide range of medications, including steroids, antihypertensives, disulfrum, and any prescription or *over-the-counter* depressant or stimulant-like substances. A similar range of medications can be associated with temporary anxiety syndromes, sexual dysfunctions, and conditions of disturbed sleep." (p. 488.)

47. Importantly, the DSM V requires the medical use of cannabis be considered before making a cannabis use disorder diagnosis, as symptoms of tolerance and withdrawal will naturally occur when a substance is taken as indicated for a medical condition and should not be used as the primary criteria for determining a diagnosis of a substance use disorder. (p. 511-512.)

48. In sum, it is my considered opinion that including marijuana and THC in Schedule I of the Controlled Substances Act is inappropriate for the following reasons:

A. Medicinal cannabis is effective for many medical conditions;

B. Medicinal cannabis can be used safely, particularly under medical supervision;

C. Medicinal cannabis is safer than the use of many other commonly used medications;

D. The major harm of cannabis use is its continued illegality.

I declare under penalty of perjury that the foregoing is true and correct, except for those matters stated on information and belief, and as to those matters I believe them to be true. This declaration signed on the 1st day of June, 2015, in Pahoa, Hawaii.

/s/ Philip A. Denney, M.D.
PHILIP A. DENNEY, M.D.

DECLARATION OF PHILIP A DENNEY, M.D.
ADDENDUM

I, Philip A. Denney, M.D., provide the following as a non-exhaustive list of recent, relevant controlled trials, case-reports, observational trials, survey data, or reviews in the peer-reviewed literature indicating the safety and efficacy of the administration of whole-plant cannabis or cannabinoids in specific patient populations. I have distinguished for this Court these research papers as they are the most informative due to the applied scientific design of the study.

1. Waissengrin B et al. 2014 Jun 14 [Epub ahead of print] Patterns of Use of Medical Cannabis Among Israeli Cancer Patients: A Single Institution Experience. *Journal of Pain Symptom Management* (2014. Doi:10.1016/j.painsymman.2014.05.018. SURVEY AND OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

2. Lotan et al., 2014. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. Clinical Neuropharmacology 37: 41-44. OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

3. Natfali et al., 2013. Cannabis Induces a Clinical Response in Patients with Crohn's Disease: a Prospective Placebo-Controlled Study. Clinical Gastroenterology and Hepatology 11: 1276-1280. CLINICAL, PLACEBO-CONTROLLED

4. Cooper et al, 2013. Comparison of the Analgesic Effects of Dronabinol and Smoked Marijuana In Daily Marijuana Smokers. Neuropsychopharmacology 38: 1984-1992. CLINICAL, PLACEBO-CONTROLLED

5. Porter and Jacobson. 2013. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy & Behavior 29: 574-577 SURVEY

6. Singh and Bali. 2013. Cannabis extract treatment for terminal acute lymphoblastic leukemia with a Philadelphia chromosome mutation. Case reports in Oncology 6: 585-592. CASE SUMMARY

7. Ravikoff et al., 2013. Marijuana use patterns among patients with inflammatory bowel disease. Inflammatory Bowel Diseases 19: 2809-2814. SURVEY

8. Penner et al. 2013. Marijuana use on glucose, insulin, and insulin resistance among US adults. American Journal of Medicine 126: 583-589. OBSERVATIONAL, CASE-CONTROL

9. Grant et al., 2012. Medical marijuana: Clearing away the smoke. The Open Neurology Journal 6: 18-25. LITERATURE REVIEW

10. Bostwick. 2012. Blurred boundaries: The therapeutics and politics of medical marijuana. Mayo Clinic Proceedings 2: 172-186. LITERATURE REVIEW

11. Passie et al., 2012. Mitigation of post-traumatic stress symptoms by Cannabis resin: a review of the clinical and neurobiological evidence. Drug Testing & Analysis 4: 649-659. CASE SUMMARY

12. Rajavashisth et al. 2012. Decreased prevalence of diabetes in marijuana users. BMJ Open 2 OBSERVATIONAL, CASE-CONTROL

13. Wilsey et al., 2012. Low-dose vaporized cannabis significantly improves neuropathic pain. The Journal of Pain 14: 136-148. CLINICAL, PLACEBO CONTROLLED

14. Corey-Bloom et al. 2012. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. Journal of the Canadian Medical Association 184: 1143-50. CLINICAL, PLACEBO-CONTROLLED

15. Riggs et al.. 2011. A pilot study of the effects of cannabis on appetite hormones in HIV-infected adult men. Brain Research 1431: 46-52. CLINICAL, PLACEBO-CONTROLLED

16. Abrams et al. 2011. Cannabinoid-opiod interaction in chronic pain. Clinical Pharmacology & Therapeutics 90: 844-851. CLINICAL, OBSERVATIONAL (NO PLACEBO GROUP)

17. Fiz et al. 2011. Cannabis use in patients with fibromyalgia: Effect on symptoms relief and health-related quality of life. PLoS One 6. OBSERVATIONAL, CASE-CONTROL

18. Lal et al. 2011. Cannabis use among patients with inflammatory bowel disease. European Journal of Gastroenterology & Hepatology 23: 891-896. SURVEY

19. Naftali et al. 2011. Treatment of Crohn's disease with cannabis: an observational study. Journal of the Israeli Medical Association 13: 455-458. OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

20. Foroughi et al., 2011. Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas--possible role of Cannabis inhalation. Child's Nervous System 27: 671-679. CASE REPORT

21. Ware et al. 2010. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 182: 694-701. CLINICAL, PLACEBO-CONTROLLED

22. Hazekamp and Grotenhermen. 2010. Review on clinical studies with cannabis and cannabinoids 2005-2009. (Special issue): 1-21 LITERATURE REVIEW

23. Robbins et al. 2009. Cluster attacks responsive to recreational cannabis and dronabinol. Headache 49: 914-916 CASE REPORT

24. Corless et al. 2009. Marijuana effectiveness as an HIV self-care strategy. Clinical Nursing Research 18: 172-193. SURVEY

25. Costain. 2008. The effects of cannabis abuse on the symptoms of schizophrenia: patient perspectives. International Journal of Mental Health Nursing 17: 227-235. SURVEY

26. Wilsey et al. 2008. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. Journal of Pain 9: 506-521. CLINICAL, PLACEBO-CONTROLLED

27. Ellis et al. 2008. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 34: 672-80. CLINICAL, PLACEBO-CONTROLLED

28. Abrams et al. 2007. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 68: 515-521. CLINICAL, PLACEBO-CONTROLLED

29. Wallace et al. 2007. Dose-dependent Effects of Smoked Cannabis on Capsaicin-induced Pain and Hyperalgesia in Healthy Volunteers. Anesthesiology 107: 785-796. CLINICAL, PLACEBO-CONTROLLED

30. Haney et al. 2007. Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep. Journal of Acquired Immune Deficiency Syndrome 45: 545-554. CLINICAL, COMPARATIVE (NO PLACEBO GROUP)

31. Rog et al. 2007. Oromucosal delta-9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clinical Therapeutics 29: 2068-2079. OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

32. Sylvestre et al. 2006. Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. European Journal of Gastroenterology & Hepatology. 18: 1057-1063. OBSERVATIONAL, CLINICAL (NO PLACEBO)

33. Pacher et al. 2006. The endocannabinoid system as an emerging target for pharmacotherapy. Pharmacological Reviews 58: 389-462. LITERATURE REVIEW

34. Chong et al. 2006. Cannabis use in patients with multiple sclerosis. Multiple Sclerosis 12: 646-651. SURVEY

35. Wade et al. 2006. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms of multiple sclerosis. Multiple Sclerosis 12: 639-645. OBSERVATIONAL, CLINICAL (NO PLACEBO GROUP)

36. Amar. 2006. Cannabinoids in medicine: A review of their therapeutic potential. Journal of Ethnopharmacology 105: 1-25 LITERATURE REVIEW

37. Woolridge et al. 2005. Cannabis use in HIV for pain and other medical symptoms. Journal of Pain and Symptom Management 29: 358-367. SURVEY

38. Rog et al. 2005. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 65: 812-819. CLINICAL, PLACEBO-CONTROLLED

39. Gorter et al. 2005. Medical use of cannabis in the Netherlands. *Neurology* 64: 917-919. SURVEY

40. Swift et al. 2005. Survey of Australians using cannabis for medical purposes. *Harm Reduction Journal* 4: 2-18. SURVEY

41. Ware et al. 2005. The medicinal use of cannabis in the UK: results of a nationwide survey. *International Journal of Clinical Practice* 59: 291-295. SURVEY

42. Brady et al. 2004. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Multiple Sclerosis 10: 425-433. CLINICAL, OBSERVATIONAL (NO PLACEBO GROUP) LITERATURE REVIEW

43. Venderova et al. 2004. Survey on cannabis use in Parkinson's disease: subjective improvement of motor symptoms. Movement Disorders 19: 1102-1106. SURVEY

44. Gross et al., 2004. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center. Neurology 62: 2095-2097. SURVEY

45. Abrams et al. 2003. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. Annals of Internal Medicine 139: 258-266. CLINICAL, PLACEBO-CONTROLLED

46. Russo et al. 2002. Chronic cannabis use in the Compassionate Investigational New Drug program: An examination of benefits and adverse effects of legal clinical cannabis. Journal of Cannabis Therapeutics 2: 3-57. CLINICAL, OBSERVATIONAL (NO PLACEBO GROUP).

47. Wallace, Mark et al. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. Journal of Pain. 2015, Apr 3. [Epub ahead of print.] RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED CROSSOVER STUDY

48. Alshaarawy, Omayma, et al. Cannabis Smoking and Diabetes Mellitus. Results from Meta-analysis with Eight Independent Replication Samples. Epidemiology. [Epub ahead of print.] SURVEY

49. Thomas, Anil A., et al. Association Between Cannabis Use and the Risk of Bladder Cancer: Results From the California Men's Health Study. Oncology. 2015 Feb;85(2):388-92. SURVEY

50. Iseger, Tabitha A. et al. A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia Research*. 2015 Mar;162(1-3):153-61. META-ANALYSIS

51. Lau, Nicholas et al. A safer alternative: Cannabis substitution as harm reduction. *Drug and Alcohol Review*. (2015.) 2015 Apr 28. [Epub ahead of print.] SURVEY

52. Finseth et al. Self reported efficacy of cannabis and other complementary medicine modalities by Parkinson's disease patients in Colorado. Evidence-Based Complementary and Alternative Medicine. 2015;2015:874849. SURVEY

53. Degenhardt et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug and Alcohol Dependence. 2015 Feb 1;147:144-50. SURVEY

54. Hussain et al. Perceived efficacy of cannabidiol enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox]Gastaut syndrome. Epilepsy & Behavior. 2015 Apr 29. SURVEY

55. Press et al. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy & Behavior. 2015 Apr;45:49-52. SURVEY

56. Amsterdam et al. European rating of drug harms. Journal of Psychopharmacology. 2015 Apr 28. SURVEY

57. Rehm, Jürgen. Fischer, Benedikt. Cannabis legalization with strict regulation, the overall superior policy option for public health. 2015 Jun;97(6):541-544. ARTICLE

58. Weiland, Barbara J. Daily Marijuana Use Is Not Associated with Brain Morphometric Measures in Adolescents or Adults. Neurobiology of Disease. 2015 Jan 28;35(4):1505-12. SURVEY

59. NHTSA. Drug and Alcohol Crash Risk. SURVEY

60. Lachenmeier, Dirk W., et al. Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. Scientific Reports. (2015.) 2015 Jan 30;5:8126. SURVEY

61. Kempker et al. Effects of Marijuana Exposure on Expiratory Airflow: A Study of Adults who Participated in the U.S. National Health and Nutrition Examination Study. Annals of the American Thoracic Society. 2015 Feb;12(2):135-41. SURVEY

EXHIBIT 2

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Greenwood, CA 95635
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Facsimile- 530-333-2165
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CURRICULUM VITAE

PERSONAL:

Age 55; Married to Latitia; Three children: Sarah, age 29, Elizabeth, age 27, Camille 19; Height 5'10"; Weight 180 lbs.

BACKGROUND:

Born in Washington, D.C.; raised in Hyattsville, MD. Father – Architect; Mother – Registered Nurse. Eldest of three brothers and four sisters. Roman Catholic primary and high school education with participation in baseball, football and boxing with Hyattsville Boys Club.

MILITARY:

U. S. Navy (1966-1972); Active Duty (1966-1970). Aircraft Emergency Equipmentman Second Class (ES), Antisubmarine Flight Crewman, Atlantic Patrol, 1,000 hours flight time. Sport parachute team member.

EDUCATION:

- Pennsylvania State University (1968)
- Bucks County Community College (1968-1971)
- Ohio University (1970-1972); Honors College (1971)
  - Board of Directors of United Campus Ministry (1971)
  - Psychiatric Technician, Athens State Hospital (1970-1972)
  - Clavine Alkaloid Research (1972)
- University of Southern California School of Medicine (1972-1976)
  - Doctor of Medicine (June 3, 1976)
  - Foothill Free Clinic (1974-1976)
  - CMA Alternate Delegate (1973-1974); CMA Delegate (1974-1975)
  - Consultant Reference Committee "B" CMA (1975)

PROFESSIONAL ACTIVITIES:

- L.A. County – USC Medical Center – Flex "A" rotating internship (1976-1977)
- Auburn Medical Clinic, Auburn, CA – Group general and family medical practice (1977-1978)
- Greenwood Medical Clinic, Greenwood, CA – Solo general and family medical practice (1978-1984)
- Sacramento Emergency Medical Group, Cordova Health Center, Rancho Cordova, CA – Urgent Care/Family practice (1984-1987)
- Med Center Medical Group, Citrus Heights, CA – Facility Medical Director, Urgent Care/Family practice (1987-1989)
- Sierra Pacific Emergency Medical Group, Mercy San Juan Hospital Satellite Facility, Carmichael, CA – Assistant Medical Director/Emergency Services (1989-1994)
- Medical Clinic of Sacramento, Sacramento, CA – Urgent Care (1994-1996)
- Meridian Occupational Medicine Group, Sacramento, CA – Facility Medical Director (1996-1997)
- Healthsouth Medical Clinic, Rocklin, CA – Facility Medical Director (1997-1999)
- Marshall Hospital – Medical Director, Marshall Center for Occupational Health (1999-2000)
- Philip A. Denney, M D – Medical Cannabis Evaluation (2000- Present)
- Medicinal Cannabis Testimony – Alameda, Alpine, Butte, El Dorado, Humboldt, Napa, Nevada, Placer, Riverside, Sacramento, San Bernardino, San Francisco, San Joaquin, Santa Clara, Shasta, Sonoma, Stanislaus, Tehama, Trinity and Tulare Counties
- Guest lecturer- USC School of Medicine- Clinical Uses of Cannabis (2005)
- Testimony Medicinal Cannabis Policy- Arkansas State Legislature (2005)

HOSPITAL PRIVILEGES:

- Auburn Faith Community Hospital – Attending staff in family medicine, pediatrics and obstetrics (1977-1985)
- Sutter General Hospital – Attending staff, family practice (1985-1987)
- Mercy San Juan Hospital – Senior staff, emergency medicine (1989-1994)
- Marshall Hospital-Courtesy staff (1999 to 2000)
- California License G34393; BNDD Number AD 7581045

PROFESSIONAL SOCIETIES:

- Society of Cannabis Clinicians- President (2006 to present)

EXHIBIT 3

EXECUTIVE ORDER NO. 6

WHEREAS, it is beyond dispute that patients suffering from debilitating medical conditions deserve to live in dignity with as little suffering as possible; and

WHEREAS, medical decisions must be based on science and health, not ideology or social policy; and

WHEREAS, scientific studies demonstrate that the medical use of marijuana has proven to be an effective treatment for patients suffering from painful, debilitating, and often chronic medical conditions; and

WHEREAS, New Jersey amended its state law to allow for the authorized medical use of marijuana with the passage of the New Jersey Compassionate Use Medical Marijuana Act in 2010; and

WHEREAS, 29 states have recently allowed the use of marijuana for medical purposes; and

WHEREAS, even a Republican-controlled Congress has repeatedly renewed the Rohrabacher-Farr Amendment, prohibiting the U.S. Department of Justice from using funds to interfere with state medical marijuana laws; and

WHEREAS, implementation of the New Jersey Compassionate Use Medical Marijuana Act was a lengthy process marked by significant delays, resulting in far fewer patients being served by the program than anticipated when the law was enacted; and

WHEREAS, there are currently five medical marijuana alternative treatment centers (ATCs) in operation in New Jersey; and

WHEREAS, only one additional ATC has been able to obtain a permit and is scheduled to begin operations in the foreseeable future; and

WHEREAS, of New Jersey's nine million residents, only approximately 15,000 are able to participate in the State's medical marijuana program; and

WHEREAS, in contrast, the medical marijuana program in Michigan, a state with a similar population to New Jersey, currently serves over 218,000 patients, and the program in Arizona, a state with a smaller population than New Jersey, serves over 136,000 patients; and

WHEREAS, the need for medical marijuana in New Jersey currently far exceeds the supply that the existing licensed ATCs in operation are able to provide; and

WHEREAS, giving patients a greater opportunity to obtain medical marijuana in accordance with State law will ensure that they are receiving a product tailored to their medical needs, and make them less likely to turn to potentially more harmful and less medically appropriate drugs such as opioids, the use of which was declared a public health crisis in Executive Order No. 219 (2017); and

WHEREAS, one study conducted by researchers at the Johns Hopkins Bloomberg School of Public Health and the Philadelphia Veterans Affairs Medical Center found that the annual number of deaths from prescription drug overdose is 25 percent lower in states where medical marijuana is legal than in states where it is illegal; and

WHEREAS, my administration is committed to fulfilling the intent, promise, and potential of the New Jersey Compassionate Use Medical Marijuana Act by providing patients in New Jersey with a well-functioning and effectively administered medical marijuana program that best serves their medical needs;

NOW, THEREFORE, I, PHILIP D. MURPHY, Governor of the State of New Jersey, by virtue of the authority vested in me by the Constitution and by the Statutes of this State, do hereby ORDER and DIRECT:

1. The Department of Health ("Department") and the Board of Medical Examiners ("Board") shall undertake a review of all aspects of New Jersey's medical marijuana program, with a focus on ways to expand access to marijuana for medical purposes. This review should include, but not be limited to:

a. An evaluation of the current rules regulating the operations and siting of dispensaries and cultivation facilities, particularly focusing on whether the rules should be revised to remove unwarranted obstructions to expansion;

b. A review of the current process for obtaining a license to operate a medical marijuana dispensary, including recommendations to expedite that process;

c. An examination of conditions for participating physicians in the program to ensure that any such requirements are not needlessly onerous;

d. An analysis of the current list of debilitating medical conditions for which medical marijuana may be authorized pursuant to N.J.S.A. 24:61-3, and a recommendation as to whether doctors should be given flexibility to make these determinations on their own;

e. An assessment of the methods through which patients or their primary caregivers are obtaining medical marijuana and a recommendation of whether rules should be amended to approve additional methods that could facilitate patient access;

f. A review of regulations that govern the forms in which medical marijuana can be ingested, taking into consideration the needs for different methods for different patients; and

g. Any other aspect of the program within the Department or the Board's discretion that hinders or fails to effectively achieve the statutory objective of ensuring safe access to medical marijuana for patients in need.

2. This review shall conclude within 60 days of this Order, at which time the Department and Board shall initiate the rulemaking process for appropriate regulatory reforms consistent with this Order.

3. This Order shall take effect immediately.

GIVEN, under my hand and seal this 23rd day of January, Two Thousand and Eighteen, and of the Independence of the United States, the Two Hundred and Forty-Second.

[seal]

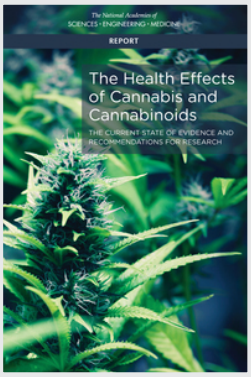
/s/ Philip D. Murphy

Governor

Attest:

/s/ Matthew J. Platkin

Chief Counsel to the Governor



The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

DETAILS

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CONTRIBUTORS

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

Summary

Over the past 20 years there have been substantial changes to the cannabis policy landscape. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days, and between 2002 and 2015 the percentage of past month cannabis users in this age range has steadily increased (CBHSQ, 2016).

Despite the extensive changes in policy at the state level and the rapid rise in the use of cannabis both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects (harms and benefits) of cannabis use remains elusive. A lack of scientific research has resulted in a lack of information on the health implications of cannabis use, which is a significant public health concern for vulnerable populations such as pregnant women and adolescents. Unlike other substances whose use may confer risk, such as alcohol or tobacco, no accepted standards exist to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively.

Within this context, in March 2016, the Health and Medicine Division

BOX S-1
Statement of Task

The National Academies of Sciences, Engineering, and Medicine (the National Academies) will appoint an ad hoc committee to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents.

The committee will develop a consensus report with two primary sections: (1) a section of the report will summarize what can be determined about the health effects of marijuana use and, (2) a section of the report will summarize potential therapeutic uses of marijuana. The report will also provide a background overview of the cannabinoid/endocannabinoid system, history of use in the United States, and the regulation and policy landscape. In addition, the report will outline and make recommendations regarding a research agenda identifying the most critical research questions regarding the association of marijuana use with health outcomes (both risks and therapeutic) that can be answered in the short term (i.e., within a 3-year time frame) as well as any steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions (e.g., appropriate questions on large population surveillance surveys, clinical data collection or other data capture, and resolution of barriers to linkage between survey data and death/morbidity registries to enable population-level morbidity and mortality effects estimates). The committee should focus on questions and consequences with the potential for the greatest public health impact, while shedding light on the characteristics of marijuana use that impact both short- and long-term health.

In conducting its work, the committee will conduct a comprehensive review of the evidence, using accepted approaches of literature search, evidence review, grading, and synthesis. Studies reviewed regarding health risks should be as broad as possible, including but not limited to epidemiology and clinical studies, and toxicology and animal studies when determined appropriate by the committee. The committee will provide summary determinations regarding causality based on strength of evidence. Both U.S. and international studies may be reviewed based upon relevance and methodological rigor.

(formerly the Institute of Medicine [IOM][1]) of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to convene a committee of experts to conduct a comprehensive review of the literature regarding the health effects of using cannabis and/or its constituents that had appeared since the publication of the 1999 IOM report

[1] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

Marijuana and Medicine. The resulting Committee on the Health Effects of Marijuana consisted of 16 experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, respiratory disease, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. The sponsors of this report include federal, state, philanthropic, and nongovernmental organizations, including the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); The Colorado Health Foundation; Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; the Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and Washington State Department of Health.

In its statement of task, the committee was asked to make recommendations for a research agenda that will identify the most critical research questions regarding the association of cannabis use with health outcomes (both harms and benefits) that can be answered in the short term (i.e., within a 3-year time frame), as well as steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions. Of note, throughout the report the committee has attempted to highlight research conclusions that affect certain populations (e.g., pregnant women, adolescents) that may be more vulnerable to potential harmful effects of cannabis use. The committee's full statement of task is presented in Box S-1.

STUDY CONTEXT AND APPROACH

Over the past 20 years the IOM published several consensus reports that focused on the health effects of marijuana or addressed marijuana within the context of other drug or substance abuse topics.[2] The two IOM reports that most prominently informed the committee's work were *Marijuana and Health,* published in 1982, and the 1999 report *Marijuana and Medicine: Assessing the Science Base.* Although these reports differed in scope, they were useful in providing a comprehensive body of evidence upon which the current committee could build.

The scientific literature on cannabis use has grown substantially since the 1999 publication of *Marijuana and Medicine.* The committee conducted an extensive search of relevant databases, including Medline, Embase,

[2] See https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana (accessed January 5, 2017).

BOX S-2
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chronic pain; cancer, chemotherapy-induced nausea/vomiting; anorexia and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis or spinal cord injury; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; dementia; glaucoma; traumatic brain injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia and other psychoses

Cancer

- Lung cancer; head and neck cancer; testicular cancer; esophageal cancer; other cancer

Cardiometabolic risk

- Acute myocardial infarction; stroke; metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes mellitus

Respiratory disease

- Pulmonary function; chronic obstructive pulmonary disorder; respiratory symptoms (including chronic bronchitis); asthma

Immunity

- Immune function; infectious disease

the Cochrane Database of Systematic Reviews, and PsycINFO, and they initially retrieved more than 24,000 abstracts that could have potentially been relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by "anonymous" authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report.

Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research for 11 groups of health endpoints (see Box S-2). For each health endpoint,

Injury and death

- All-cause mortality; occupational injury; motor vehicle crash; overdose injury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy complications for the mother; fetal growth and development; neonatal conditions; later outcomes for the infant

Psychosocial

- Cognition (learning, memory, attention, intelligence); academic achievement and educational outcomes; employment and income; social relationships and other social roles

Mental health

- Schizophrenia and other psychoses; bipolar disorders, depression; suicide; anxiety; posttraumatic stress disorder

Problem cannabis use

- Cannabis use disorder

Cannabis use and abuse of other substances

- Abuse of other substances

systematic reviews were identified and assessed for quality using published criteria; only fair- and good-quality reviews were considered by the committee. The committee's conclusions are based on the findings from the most recently published systematic review and all relevant fair- and good-quality primary research published after the systematic review. Where no systematic review existed, the committee reviewed all relevant primary research published between January 1, 1999, and August 1, 2016. Primary research was assessed using standard approaches (e.g., Cochrane Quality Assessment, Newcastle–Ontario scale) as a guide.

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame while adhering to the National

Academies' high standards for the quality and rigor of committee reports. Readers of this report should recognize two important points. First, the committee was not tasked to conduct multiple systematic reviews, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search; assessments by more than one person of the quality (risk of bias) of key literature and the conclusions; prespecification of the questions of interest before conclusions were formulated; standard language to allow comparisons between conclusions; and declarations of conflict of interest via the National Academies conflict-of-interest policies. Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time frame available to the committee. Furthermore, very good research may not be reflected in this report because it did not directly address the health endpoint research questions that were prioritized by the committee.

This report is organized into four parts and 16 chapters. Part I: Introduction and Background, Part II: Therapeutic Effects (Therapeutic Effects of Cannabis and Cannabinoids), Part III: Other Health Effects, and Part IV: Research Barriers and Recommendations. In Part II, most of the evidence reviewed in Chapter 4 derives from clinical and basic science research conducted for the specific purpose of answering an a priori question of whether cannabis and/or cannabinoids are an effective treatment for a specific disease or health condition. The evidence reviewed in Part III derives from epidemiological research that primarily reviews the effects of smoked cannabis. It is of note that several of the prioritized health endpoints discussed in Part III are also reviewed in Part II, albeit from the perspective of effects associated with using cannabis for primarily recreational, as opposed to therapeutic, purposes.

Several health endpoints are discussed in multiple chapters of the report (e.g., cancer, schizophrenia); however, it is important to note that the research conclusions regarding potential harms and benefits discussed in these chapters may differ. This is, in part, due to differences in the study design of the reviewed evidence, differences in characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report's chapters. In drafting the report's conclusions, the committee made an effort to be as specific as possible about the type and/or duration of cannabis or cannabinoid exposure and, where relevant, cross-referenced findings from other report chapters.

REPORT CONCLUSIONS ON THE ASSOCIATION BETWEEN CANNABIS USE AND HEALTH

From their review, the committee arrived at nearly 100 different research conclusions related to cannabis or cannabinoid use and health. Informed by the reports of previous IOM committees,[3] the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoid use (for therapeutic purposes) is an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) is statistically associated with the prioritized health

[3] *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence* (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

BOX S-3
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

continued

BOX S-3 Continued

MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

endpoints of interest. Box S-3 describes these categories and the general parameters for the types of evidence supporting each category. For a full listing of the committee's conclusions, please see this chapter's annex.

REPORT RECOMMENDATIONS

This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. The committee has put forth a substantial number of research conclusions on the health effects of cannabis and cannabinoids. Based on their research conclusions, the committee members formulated four recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. The report's full recommendations are described below.

Address Research Gaps

***Recommendation 1*: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies,[4] philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:**

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youth (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and THC or other cannabinoids.
- Determine the harms and benefits associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential beneficial and harmful health effects of using different forms of cannabis, such

[4] Agencies may include the CDC, relevant agencies of the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA).

as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.
- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

Improve Research Quality

***Recommendation 2*: To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), agencies of the U.S. Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention, should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:**

- The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.

- Adaptation of existing research-reporting standards to the needs of cannabis research.
- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

Improve Surveillance Capacity

***Recommendation 3*: To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:**

- The development of question banks on the beneficial and harmful health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and the National Survey of Family Growth.
- Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., *International Classification of Diseases-10*).
- The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
- The development of novel diagnostic technologies that allow for rapid, accurate, and noninvasive assessment of cannabis exposure and impairment.
- Strategies for surveillance of harmful effects of cannabis for therapeutic use.

Address Research Barriers

***Recommendation 4*: The Centers for Disease Control and Prevention, National Institutes of Health, U.S. Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:**

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

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ANNEX

Report Conclusions[5]

Chapter 4 Conclusions—Therapeutic Effects of Cannabis and Cannabinoids

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

[5] Numbers in parentheses correspond to chapter conclusion numbers.

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

Chapter 5 Conclusions—Cancer

There is moderate evidence of *no* statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

Chapter 6 Conclusions—Cardiometabolic Risk

There is limited evidence of a statistical association between cannabis use and:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:

- The increased risk of acute myocardial infarction (6-1b)

Chapter 7 Conclusions—Respiratory Disease

There is substantial evidence of a statistical association between cannabis smoking and:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

Chapter 8 Conclusions—Immunity

There is limited evidence of a statistical association between cannabis smoking and:

- A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of *no* statistical association between cannabis use and:

- The progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV) (daily cannabis use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

Chapter 9 Conclusions—Injury and Death

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, nonmedical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

Chapter 10 Conclusions—Prenatal, Perinatal, and Neonatal Exposure

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

Chapter 11 Conclusions—Psychosocial

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from* cannabis use and:

- Impairments in the cognitive domains of learning, memory, and attention (11-1b)

Chapter 12 Conclusions—Mental Health

There is substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)

- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

Chapter 13 Conclusions—Problem Cannabis Use

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)

- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

Chapter 14 Conclusions—Cannaabis Use and the Abuse of Other Substances

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

Chapter 15 Conclusions—Challenges and Barriers in Conducting Cannabis Research

There are several challenges and barriers in conducting cannabis and cannabinoid research, including

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

Part I

Introduction and Background

EXHIBIT 4

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations ...

EXHIBIT 5

Cannabinopathic Medicine

by

Lester Grinspoon, MD

An update to *Whither Medical Marijuana published in Contemporary Drug Problems*, volume 27, Spring, 2000)

With the passage of the Marijuana Tax Act of 1937, physicians first became severely constrained in their ability to prescribe cannabis as a medicine and, as a consequence, over the next three or four decades became increasingly ignorant of both its remarkable therapeutic utility and limited toxicity. Pari passu with the explosive growth of the use of marijuana as a recreational drug in the 60s, many users serendipitously rediscovered its usefulness for a variety of medical problems. By the mid-90s, its popularity as a medicine became so great that states, beginning with California in 1996, began to make its use legal for specified medical conditions. At present 23 states and the District of Columbia allow for its use as a medicine, despite the fact that the federal government still considers it a most dangerous substance. This rapid growth of marijuana as a medicine has occurred in the face of the threat of punishment by the federal government. Furthermore, it cannot be legally sold as a medicine because the US government will not remove cannabis from Schedule I of the 1970 Comprehensive Drug Abuse and Control Act ; this precludes the possibility of acquiring the research data which is needed before a drug can be approved by the Food and Drug Administration (FDA)) for commercial distribution . The government will, sooner or later, abandon its archaic view of cannabis and this will legitimize the use of marijuana as a medicine: this will not, however, ensure its rightful place in the pharmacopeia of modern Western medicine (allopathic medicine). The American Medical Association's House of Delegates in their November, 2013 meeting voted to retain their long-standing position that "cannabis is a dangerous drug and as such is a public health concern." Should modern medicine persist in ignoring the use of cannabis as a medicine, this growing practice will surely continue to develop, perhaps into a school or philosophy of medicine which might be referred to as cannabinopathic medicine.

A native of Central Asia, cannabis (hemp) may have been cultivated as long as 10,000 years ago. It was certainly cultivated in China by 4000 BC and in Turkestan by 3000

BC. It has long been used as a medicine in India, China, the Middle East, Southeast Asia, South Africa, and South America. In an herbal published during the reign of the Chinese emperor Chen Nung 5000 years ago cannabis was recommended for malaria, constipation, rheumatic pains, "absentmindedness" and "female disorders." One Chinese herbalist recommended a mixture of hemp, resin, and wine as an analgesic during surgery. In India cannabis had been recommended to quicken the mind, lower fevers, induce sleep, cure dysentery, stimulate appetite, improve digestion, relieve headache, and cure venereal disease. In Africa it was used for dysentery, malaria, and other fevers. Today certain tribes treat snakebite with hemp or smoke it before childbirth. Hemp was also noted as a remedy by Galen and other physicians of the classical and Hellenistic eras, and it was highly valued in medieval Europe. The English clergyman Robert Burton, in his famous work *The Anatomy of Melancholy,* published in 1621, suggested the use of cannabis in the treatment of depression. The *New English Dispensatory* of 1764 recommended applying hemp roots to the skin for inflammation, a remedy that was already popular in Eastern Europe. The *Edinburgh New Dispensary* of 1794 included a long description of the effects of hemp and stated that the oil was useful in the treatment of coughs, venereal disease, and urinary incontinence.

However, in the West cannabis did not come into its own as a medicine until the mid-19th century. The first Western physician to take an interest in cannabis as medicine was W.B. O' Shaughnessy, a young professor at the Medical College of Calcutta, who had observed its use in India. He gave cannabis to animals, satisfied himself that it was safe, and began to use it with patients suffering from rabies, rheumatism, epilepsy, and tetanus. In a report published in 1839, he wrote that he had found *Cannabis Indica* (a solution of cannabis in alcohol, taken orally) to be an effective analgesic. He was also impressed with its muscle-relaxant properties and called it "an anticonvulsive remedy of the greatest value."

O'Shaughnessy returned to England in 1842 and provided cannabis to pharmacists. Doctors in Europe and the United States soon began to prescribe it for a variety of physical conditions. Cannabis was even given to Queen Victoria for the treatment of her painful pre-menstrual cramps by her court physician. It was admitted to the United States Pharmacopeia in 1850, and commercial cannabis preparations soon became widely distributed through drugstores. Pharmacies welcomed the arrival of this "new" medicine, *Cannabis Indica,* because at that time their shelves held few truly effective drugs to offer the practitioners of allopathic medicine. As its use became increasingly widespread, clinical reports on cannabis accumulated, and by the turn of the century more than 100 papers had been published in the Western medical literature recommending it for various illnesses and discomforts and extolling its remarkably limited toxicity.

The decline in the usage of *Cannabis Indica* began toward the end of the century. Both the potency of cannabis preparations and its absorption from the bowel were too variable, and individual responses to orally ingested cannabis seemed erratic and unpredictable. Another reason for the neglect of research on the analgesic properties of cannabis was the greatly increased use of opiates after the invention of the hypodermic syringe in the 1850s allowed soluble drugs to be injected for fast relief of pain; cannabis products are insoluble in water and so cannot easily be administered by injection. The end of the 19th century saw the development of such synthetic drugs as aspirin, chloral hydrate, and barbiturates. Two of the most common symptoms for which *Cannabis Indica* was prescribed were pain and insomnia, and now physicians could prescribe

easy-to-take pills of known potency for these two problems, hastening the decline of cannabis as a medicine. But the new drugs had striking disadvantages. More than 1000 people die from aspirin-induced bleeding each year in the United States, and barbiturates are, of course, far more dangerous.

But the Marijuana Tax Act of 1937 was the ultimate death-knell for *Cannabis Indica.* This law was the culmination of a campaign organized by the Federal Bureau of Narcotics under Harry Anslinger in which the public was led to believe that cannabis, now commonly referred to as marijuana, was addictive and that its use led to violent crimes, psychosis, and mental deterioration; it is now confined to Schedule I under the Controlled Substances Act of 1970 as a drug that has a high potential for abuse, lacks accepted medical use, and is unsafe for use even under medical supervision. The film *Reefer Madness,* made as part of Anslinger's campaign, may be a joke to the sophisticated today, but it was once regarded as a serious attempt to address a social problem; the atmosphere and attitudes it exemplified and promoted continue to influence our culture, albeit much less so today. The Marijuana Tax Act was not directly aimed at the medical use of cannabis; its purpose was to discourage recreational marijuana smoking. Almost incidentally the law made medical use of cannabis difficult because of the extensive paperwork and fees required of doctors who wanted to prescribe it. The Federal Bureau of Narcotics followed up with "anti-divergent" regulations that contributed to physicians' disenchantment. Its removal from the United States Pharmacopeia and the National Formulary in 1942 signaled both the end of physicians' interest in and allopathic medicine's institutional embrace of cannabis. Furthermore, physicians allowed themselves to become ignorant about this drug as they have, since the mid-1930s, been increasingly exposed along with every other citizen to the deceptive propaganda against marijuana propagated by the United States government and such private organizations as the Partnership for a Drug Free America.

The concept of marijuana as a medicine virtually disappeared for several decades. Then in the 1960s, as large numbers of people began to use marijuana recreationally, claims of its medical utility began to appear, not in the medical literature but in the form of letters to popular magazines like *Playboy*. Typically these accounts were written by surprised and excited recreational users who had serendipitously discovered that marijuana relieved one or another of a variety of symptoms and syndromes. Over the next several decades, the grapevine word of these rediscovered medical utilities continued to grow. With the advent of the AIDS epidemic and the discovery of marijuana's ability to reduce the nausea and therefore the threat of the "weight reduction syndrome of AIDS", this reappearance of the concept of cannabis as a medicine gathered enough momentum to be publicly palpable. It was at this time that public pressure on the government to reconsider its obdurately held position developed in earnest, but with little success to date at the federal level.

There is an important difference in the way cannabis was used as a medicine in the latter half of the 19th century and the way it has been generally administered since its reemergence as a *sub rosa* medicine in the mid-20th century. In its earlier iteration it was dispensed orally as an alcoholic solution; now it is primarily taken through the pulmonary system, vaporized or as smoke. The emergence of cannabis as a recreational drug began in the early part of the 20th century and has continued to grow. One of the reasons it has grown to the point where it can now be considered a part of Western culture is its introduction as a smokable drug. A good deal of mystery and uncertainty surrounds the story of the "reefer's" debut in the United States. It is

generally thought that in the early decades of the 20th century the custom of smoking "the weed" in cigarette form traveled with groups of itinerant Mexican workers across the border in the southern and southwestern states; it is now overwhelmingly the mode of administration used by the millions who use it as a medicine or for any other reason.

This change in the route of administration has greatly enhanced its usefulness as a medicine because it solved the problem of providing the correct dose. One of the major problems that doctors in the 19th century faced with *Cannabis Indica* was that there were no reliable bioassays at that time and so physicians could never be sure that they had prescribed the correct dose. If too much were prescribed, the patient might experience discomfort in the form of anxiety, but this would not be immediately evident because it takes about one to two hours for the effects of orally administered cannabis to be experienced. However, because physicians of the 19th century understood that this was a drug of unusually limited toxicity, they were not as concerned about overdosing as they were about providing an inadequate dose. The major advantage of smoking is the rapidity with which the medicinal effect appears; symptom relief will occur in a matter of minutes. And perhaps even more importantly, this very rapid feedback allows the patient to titrate his own dose for his particular symptom with much more precision than can his physician. He just leisurely puffs until one of two things happens: he either begins to experience symptom-relief or he becomes somewhat high or anxious, at which point he stops. It is no longer believed that the smoke from marijuana is harmful to pulmonary or oropharyngeal tissues. But, for those patients who prefer not to smoke, there now is the option of using an instrument called a vaporizer which allows one to inhale the cannabinoids free of the combustion products of the cannabis plant.

In what may be the first attempt to reestablish the place of cannabis in mainstream Western medicine, the National Organization for the Reform of Marijuana Laws (NORML) in 1972 petitioned the Bureau of Narcotics and Dangerous Drugs, later renamed the Drug Enforcement Administration (DEA), to transfer marijuana from Schedule I to II so that the research necessary for the Food and Drug Administration (FDA) approval could be undertaken. Without this approval it cannot be clinically researched nor can it be legally prescribed. As the proceedings continued, other parties joined, including the Physicians Association for AIDS Care. It was only in 1986, after many years of legal maneuvering, that the DEA acceded to the demand for public hearings required by law. During the hearings, which lasted two years, many patients and physicians testified and thousands of pages of documentation were introduced. In 1988 the DEA's own Administrative Law Judge, Francis L. Young, declared in his opinion that marijuana in its natural form fulfilled the legal requirement of currently accepted medical use in treatment in the United States. He added that it was "one of the safest therapeutically active substances known to man." His order that the marijuana plant be transferred to Schedule II was overruled, not by any medical authority, but by the DEA itself, which issued a final rejection of all pleas for reclassification in March 1992.

Meanwhile, growing demand forced the FDA to institute the Individual Treatment IND (commonly referred to as a Compassionate IND) for the use of physicians whose patients needed marijuana. The application process was made enormously complicated, and most physicians did not want to become involved, especially since many believed there was some stigma attached to prescribing marijuana. Between 1976 and 1988 the government reluctantly awarded about a half-dozen Compassionate

INDs for the use of marijuana. In 1989 the FDA was deluged with new applications from people with AIDS, and the number granted rose to 34 within the year. In June 1991, the Public Health Service announced that the program would be suspended because it undercuts the Administration's opposition to the use of illegal drugs. After that no new Compassionate IND's were granted, and the program was discontinued in March 1992. The surviving two patients are still receiving marijuana under the original program; for everyone else it is at the federal level an outlaw medicine.

Despite its federal illegality, beginning in 1996 with California's passage of its Proposition 215, 23 other states and the District of Columbia have established legislation which makes it possible for patients suffering from a variety of disorders to use the drug legally with a recommendation from a physician. Unfortunately, because most of them are so restrictive in their specifications of which symptoms and syndromes may be lawfully treated with cannabis, many patients with legitimate claims to the therapeutic usefulness of this plant must continue to use it illegally and therefore endure the extra layer of anxiety imposed by its illegality. California and Colorado are the two states in which the largest number of patients for whom it would be medically useful have the freedom to access it legally. New Jersey appears to be shaping up as one of the most restrictive, and for that reason it is likely that only a small fraction of the pool of patients who would find marijuana to be as or more useful than the invariably more toxic conventional drugs it will displace will be allowed legal access to it. The framers of the New Jersey legislation may fear what they see as chaos in the distribution of medical marijuana in California and Colorado, a fear born of their concern that the more liberal parameters of medical use adopted in these states have allowed its access to many people who use it for other than strictly medical reasons.

Because so many people are now having an opportunity to observe relatives or friends who are successfully, safely and relatively inexpensively using marijuana as a medicine, it will not be long before an overwhelming majority of citizens demand the same rights. There are now six other states working on medical marijuana legislation; this is a reflection of recent polls which show that more than 70% of American citizens now support the legal availability of marijuana as a medicine. These additional states and their citizens will inadvertently become part of an ongoing large social experiment in how best to deal with the reinvention of the "cannabis as medicine" phenomenon. Already we have learned a great deal from this ongoing experiment; one of the most important lessons is that the states which have the more restricted and limited medical indications for allowable use of marijuana as a medicine have the largest number of patients who are compelled to use it illegally, while those which are the least restricted with respect to allowable medical indications inadvertently provide it to many people who use it for other purposes.

Shortly after O' Shaughnessy introduced cannabis as a new medicine, modern Western medicine (allopathic medicine) signaled its acceptance when it was entered into the various Western pharmacopeia in the mid-19th century. It was expected, certainly by the 1990s, that it would be readmitted as a legitimate medicine, given the mountain of largely anecdotal evidence which establishes both its efficacy and safety, and its potential (once free of the prohibition tariff) to be much less expensive than pharmaceutical industry products it will replace. The two major agencies of this resistance to its readmission are the US government and the medical/pharmaceutical establishment.

EXHIBIT 5

Today drugs must undergo rigorous, expensive and time-consuming research to win approval by the FDA before they can be marketed as medicines. The first step made in trying to move the federal government was to petition it to move cannabis from its Schedule I status in the Controlled Substances Act to Schedule II so that it would then be possible to do the kinds of controlled studies essential to the presentation of any new drug to the FDA for approval in accordance with the protocol used by the pharmaceutical industry. As noted above, the first attempt to petition the FDA and DEA to move marijuana to Schedule II was initiated in 1972 and after two decades of hearings and delays the DEA rejected all pleas for reclassification. Another two decades have passed and, with the exception of a handful of small-to-medium-sized randomized controlled trials of smoked cannabis in chronic pain, spasticity, and wasting syndrome, the federal government continues to block the possibility of demonstrating that marijuana could satisfy the FDA criteria for a safe and efficacious addition to the pharmacopeia by continuing to insist, against overwhelming evidence to the contrary, that it is properly placed in Schedule I. In actuality it is now clear that marijuana no more belongs in Schedule I than does aspirin.

The purpose of the FDA testing is to protect the consumer by establishing both safety and efficacy. First, the drug's safety (or rather, limited toxicity) is established through animal and then human experiments. Next, double-blind controlled studies are conducted to determine whether the drug has more than a placebo effect and is more useful than an available drug for a particular symptom or syndrome. As the difference between drug and placebo may be small, large numbers of patients are often needed in these studies for a statistically significant effect. Medical and governmental authorities insist that before marijuana is made legally available to patients, this kind of study should be performed for each of the indications for which it is proposed to be used (labels). At the same time, the government refuses to reconsider its inappropriate assignment of marijuana to Schedule I, therein making it impossible, by imposing a tight and heavily controlled monopoly on research-approved cannabis production and distribution, to undertake the kind of studies presently demanded by the FDA for its reintegration into modern Western medicine.

But with the accumulation of an enormous amount of anecdotal evidence, it has now become doubtful whether these FDA rules should apply to marijuana. There is now little question about its safety. It has been used for thousands of years by millions of people with very little evidence of significant toxicity. Similarly, no further double-blind studies are needed to prove marijuana's efficacy. Any astute clinician who has some knowledge of the accumulated clinical experience of patients who have used marijuana as a medicine knows that it is efficacious to some degree for many people with various symptoms and syndromes. Anecdotal evidence commands much less attention than it once did, yet it is the source of much of our knowledge of synthetic medicines as well as plant derivatives. Controlled experiments were not needed to recognize the therapeutic potential of chloral hydrate, barbiturates, aspirin, curare, insulin, or penicillin--- pharmaceuticals introduced before the double-blind controlled study was invented.

Anecdotes present a problem that has always haunted medicine: the anecdotal fallacy or the fallacy of enumeration of favorable circumstances (counting the hits and ignoring the misses). If many people suffering from, say, muscle spasms caused by multiple sclerosis take marijuana and only a few get much better relief than they could get from conventional drugs, those few patients would stand out and come to our attention. They and their physicians would understandably be enthusiastic about marijuana and might

proselytize for it. These people are not dishonest, but they are not dispassionate observers. Therefore, some may regard it as irresponsible to suggest on the basis of anecdotes that cannabis may help people with a variety of disorders. That might be a problem if cannabis were a dangerous drug but, in fact, it is remarkably safe. Even in the unlikely event that only a few people with multiple sclerosis find that it provides relief from muscle spasm, it can be argued that cannabis should be available to them because the risks are so small and it costs so little to produce.

The benefits of any medicine must be weighed against the risks. Fortunately, there is unusually good evidence on the potential health hazards of marijuana---far better than the evidence on most prescription drugs. Not only has cannabis been used for thousands of years by many millions of people, but there is much recent research on its safety inspired by the federal government's interest in discovering toxic effects to justify its policy of prohibition. The potential dangers of marijuana when taken for pleasure and its possible usefulness as a medicine are historically and practically interrelated issues: historically, because the arguments used to justify the suppression of recreational use have had a disastrous influence on views of its medical potential; practically, because it is more likely to be safe as a medicine if it is relatively safe as a euphoriant. As the evidence makes it increasingly clear that cannabis is relatively benign, it is becoming more and more difficult to deny that a risk-benefit analysis now satisfies all requirements for medical use.

Penicillin was discovered in 1928 but the discovery was ignored by the medical establishment for more than a decade until the first clinical trial with six patients who suffered from a variety of infections; all were successfully treated. After this debut in 1941, penicillin rapidly earned the reputation as the wonder drug of the 1940s. It earned that reputation for three reasons: it was remarkably non-toxic, even at high doses; it could be produced inexpensively on a large scale; and it was extremely versatile, acting against microorganisms that cause a great variety of diseases, from pneumonia to syphilis. In all three respects cannabis suggests parallels: it is remarkably safe; once it is free of the prohibition tariff it will be inexpensive; and it is effective against a large number of symptoms and syndromes. Penicillin did not undergo modern FDA approval scrutiny because its safety and efficacy had been well established by the time the FDA adopted the present protocol for approving new drugs. Marijuana is now in the same position vis-à-vis the FDA; it has accumulated, both from recreational and medicinal use, more than enough evidence of its safety and efficacy.

As marijuana's reputation as a medicine grew, so did the demand for legal access. In 1996, as noted above, California became the first state to provide legal (as far as the state was concerned) access for specified signs and symptoms. Over the next 18 years 22 other states and the District of Columbia followed suit, but the defined parameters of availability, particularly the rules for distribution and the medical reasons for which use would be allowed, have generally become more constricted. In these states the only involvement with the medical establishment is the requirement that the patient receive a note from a physician stating that he believes the patient's condition would be helped by cannabis; these notes allow the patient to receive a state-issued medical marijuana registration card which may cost $100 or more annually. Each state establishes its own rules for the growing and dispensing of medical marijuana. These states now allow thousands of people to legally purchase a growing variety of marijuana products upon the presentation of these cards or, in some states, the physician's letter to one of the state-sanctioned dispensaries. It is estimated that 2 1/2 to 3% of the residents of

California are now credentialed to buy marijuana legally in what is estimated to be between a 1 1/2 to 2 1/2 billion dollar business. One has only to visit one of the California dispensaries to see how sophisticated this industry is becoming, with a range of newly developed cannabis products as well as newly invented delivery means. Beyond having perhaps several dozen or more different strains of herbal cannabis to choose from, there is a large choice of edible and even topical marijuana medications. The patient who wants to use a pipe, bong, vaporizer or vape stick will find a large and growing selection to choose from. There now exist a few laboratories equipped to measure the percentage of individual cannabinoids and terpenes, and to provide assurance against contamination with insecticides, fungi or bacteria. The rapidly increasing number of patients who are now seeking cannabis as a medicine is fueling a burgeoning medical marijuana enterprise which is becoming increasingly sophisticated. There are growers who are becoming more adept at breeding new strains which may be more beneficial to patients with particular needs, as for example the present effort to develop strains high in cannabidiol (CBD, a non-psychoactive cannabinoid).

Despite harassment by the federal authorities, especially in California and Colorado, all aspects of this alternative medicine, which is beginning to resemble a new school or philosophy of medicine, will continue to grow and become more sophisticated as it is embraced by more and more patients, legally or illegally. This new medicine arose from the past and the still growing collection of anecdotal evidence. It is now bolstered by the fundamental understandings in biology and physiology that have come from the discovery and study of the endogenous cannabinoid signaling system (the endocannabinoid system). All of this is developing outside of allopathic medicine (modern Western medicine); in what may be called "cannabinopathic medicine". It joins other alternative schools of medicine such as naturopathic medicine, homeopathic medicine and osteopathic medicine. Cannabinopathic medicine is being practiced all over this country, openly in the states which have made it legal, and clandestinely in those which have yet to do so. Osteopathic medicine, which was first practiced in the latter part of the 19th century, has now moved so close to allopathic medicine in its education, training and practice that it has become integrated with allopathic medicine. In the early days of medical marijuana it was assumed that it would become integrated into Western medicine as a new therapeutic; thus the effort which began in 1972 to persuade the federal government to change its Controlled Substances Act Schedule I status to Schedule II as the essential first step toward collecting the kind of data necessary for the FDA's medicinal drug approval process. The government has in the past made tentative moves in the direction of accepting the reality of marijuana's medical capacities, including the now defunct Compassionate IND program and its mid-80s involvement with dronabinol (Marinol), a pharmaceutical industry-developed synthetic THC which is the same 21 carbon molecule as the tetrahydrocannabinol (THC) produced by nature.

Today, even if it were free of its Schedule I chains, its path to legitimacy as a pharmaceutical faces other obstacles. A big one is the availability of funding for the kind of research which would allow it to be presented to the FDA. The cost of this research runs to upwards of $800 million per drug. Because, as a plant, it cannot be patented, the pharmaceutical companies have no interest in herbal marijuana. Only in the case of some orphan drugs does the government support these developmental costs. As noted above, an exception to this rule occurred in the early 1980s when the government provided major funding to a small pharmacedeutical company, Unimed, towards its development of the synthetic tetrahydrocannabinol Marinol. Because it cannot be

marketed as a Schedule I drug, the government placed it in Schedule II despite the fact that this THC is precisely the same molecule that is found in marijuana which it will not release from Schedule I. Several years later, because Marinol was not selling as well as was originally hoped, it was placed in the even less restrictive Schedule III. The government assumed that with Marinol's legal availability it would then be possible to assert that there was no longer a need for medicinal marijuana as there was now a commercially available cannabinoid pharmaceutical product. The problem with this strategy became obvious to nearly every patient who tried to substitute Marinol for smoked or ingested marijuana: it simply did not work nearly as well as herbal marijuana. It is becoming increasingly clear that the salutary properties of marijuana do not reside exclusively in THC but are due to an ensemble effect of herbal components including THC, cannabadiol (CBD) and terpenes. The primary reason that some patients use Marinol today is because it is legal; it appears to be as safe as herbal marijuana, but not nearly as efficacious.

The majority of people who use cannabis as a medicine must suffer the anxiety, uncertainty, and risk associated with obtaining and using an illegal substance. The responses of physicians, as indicated by patients' stories, vary a great deal. With the exception of a small minority of physicians, their attitudes toward marijuana as a medicine generally range from outspokenly negative to varying degrees of skepticism; a few are hostile or contemptuous, some are indifferent or unconvinced, and a growing number offer at least some encouragement or moral support. Unfortunately, even the most sympathetic are either afraid to do more because of the law or are unable to provide advice because they have been misinformed about cannabis and simply know too little about its therapeutic value. Physicians of one and a half centuries ago knew much more about cannabis than do contemporary physicians, whose education about new drugs comes largely from the pharmaceutical industry. Today's physicians are often introduced to therapeutic marijuana by their patients, but even those physicians who become educated about this drug may be afraid to recommend what they know or suspect to be the best treatment out of fear that they might lose their reputations, licenses, and careers. Even if marijuana were available as a Schedule II medicine, pharmacies would be reluctant to carry it and physicians would hesitate to prescribe it. Through computerized monitoring, the DEA could know who was receiving prescription marijuana and how much. It could identify physicians who, by its standards, prescribed cannabis too freely or for reasons it considered unacceptable. The potential for harassment would be extremely discouraging. Unlike other Schedule II drugs, such as cocaine and morphine, cannabis has many potential medical uses rather than just a few. Many people would undoubtedly try to persuade their doctors that they had a legitimate claim to a prescription. Doctors would not want the responsibility of making such decisions if they were constantly under threat of discipline by the DEA. Furthermore, many doctors would not consider prescribing cannabis at all because they are victims of the government's misinformation campaign. Some still believe and promote such hoary myths as the notion that marijuana is addictive or leads to the use of more dangerous drugs.

Despite the growing appreciation of its safety and usefulness as a medicine there is, after more than three decades of effort, little hope that herbal marijuana will soon be integrated into modern Western medicine. And even if it were, there would be enormous problems in controlling the distribution of a controlled medicine which has now become an established and popular Western culture recreational drug The pharmaceutical industry will continue to develop cannabinoid products and the government will

hypocritically make Controlled Substances Act scheduling accommodations, as they did with Marinol, to make them available as prescription drugs. Some of them will be useful and a few may, for specific symptoms or syndromes, be more useful than herbal marijuana, but it is unlikely that they will ever displace it; herbal marijuana will always provide more choice, be less expensive and more readily available. Because the commercial success of its cannabinoid products will vary directly with the severity of the prohibition, the pharmaceutical industry will predictably put even more pressure on the government to maintain or even strengthen its prohibition.

Perhaps in part because so many Americans have discovered for themselves that marijuana is both relatively benign and remarkably useful, moral consensus about the evil of cannabis is becoming uncertain and shallow. The authorities pretend that eliminating marijuana traffic is like eliminating slavery or piracy, or eradicating smallpox or malaria. The official federal government view is that everything possible has to be done to prevent everyone from ever using marijuana, even as a medicine. But there is also an informal lore of marijuana use that is far more tolerant. Many of the millions of cannabis users in this country not only disobey the drug laws but feel a principled lack of respect for them. They do not conceal their bitter resentment of laws that render them criminals. They believe that many people have been deceived by their government, and they have come to doubt that the "authorities" understand much about either the deleterious or the useful properties of this drug. This undercurrent of ambivalence and resistance in public attitudes towards marijuana leaves room for the possibility of change, especially since the costs of prohibition are so high and rising.

Because multifaceted marijuana is now here to stay as a very useful and safe medicine, as a superior recreational drug, and as an enhancer of a variety of human capacities, this more than 75-year-old destructive prohibition cannot endure much longer. It is reasonable to assume that had there never been a marijuana prohibition, smoked marijuana, because it is both more reliable and easier to titrate, would have displaced *Cannabis Tincture* as the cannabinoid medicine of choice. Without prohibition, marijuana would have become as easily accessible as aspirin. It would have provided the first opportunity for herbal marijuana to compete with pharmaceutical products and its success would have been assured. But now, even with the termination of the prohibition against herbal marijuana, which is now inevitable, will it regain its rightful place in modern medicine? Given the enormous influence of contemporary big Pharma on the medical establishment and the government, this is not so clear. It is presently rapidly growing as a very useful and safe medicine, which is being largely ignored by allopathic medicine. It is as though we are now witnessing the birth of a new school of medicine – – – cannabinopathic medicine.

Perhaps the most interesting question about the future of cannabinopathic medicine is whether it will continue to develop on its own as an alternative medicine with its growing literature, newly developed strains, edible and other products, delivery devices, publications, experience and experts, or whether it will be absorbed into modern Western medicine much as did one branch of osteopathy. To the extent that cannabinopathic medicine continues to exist as an entity it will be adjunctive to allopathic medicine as it will be limited to therapy, mostly as a palliative, and possibly and possibly as a preventative. Presently, its only connection to allopathic medicine is the requirement by the states in which cannabis is legally available as a medicine for the patient to first present to the state authorities a letter from a physician stating that the patient has a need for cannabis in the treatment of a health problem specified in that

particular state's medical marijuana law. Not all physicians are willing to provide such a letter and many who do, know very little about cannabis. Unfortunately, among these physicians there are some who, for a fee, are willing to sign such a letter with little or no attempt to verify either the presenting medical problem or the appropriateness of cannabis for that symptom or syndrome.

Invariably, when a newly discovered substance even hints at having therapeutic value, a pharmaceutical company will immediately do some preliminary testing to satisfy itself that it may be both safe and efficacious for a particular health problem. Once satisfied that it does, it will, if it is not an in-house discovery, acquire it and then seek the 20 year new drug patent. Once it has the patent, it will undertake the protocol for developing the data which the FDA demands before it will allow the drug to be licensed for sale. Fulfilling the demands of this protocol may take upwards of $800,000,000 and as long as up to three years. FDA approval will then allow the company to use the remaining 17 years of the patent to recover its developmental costs and earn a profit. This is the way most new drug products enter the pharmaceutical marketplace.

Needless to say, the pharmaceutical industry is aware of the therapeutic value of herbal cannabis and is increasingly devoting resources to the development of cannabinoid analogs or other products which can compete with herbal marijuana. The industry is mindful not just of the profits that such products would ensure, but as well the losses it will incur as many of its own products are displaced by the less expensive and less toxic herbal marijuana and its products. But the drug companies are stymied because it is not possible to patent a naturally occurring substance. They have produced several synthetic cannabinoids: dronabinol (Marinol) and nabilone (Cesamet), and what is best described as liquid marijuana (Sativex), which is a liquid solution of two (THC and CBD) naturally occurring cannabinoids in a patented delivery system. None of these products is as inexpensive or useful as ingested or smoked (or vaporized) herbal marijuana. Legality, not efficacy, is their major appeal. Patients who are sophisticated about cannabinopathic medicine and live in the growing number of states where it is legal to use herbal marijuana or its products generally prefer it to the pharmaceutical cannabinoids for a number of reasons: it is more efficacious, where we already will call less toxic and less expensive; and also because when it is smoked or vaporized, it is very easy for the patient to titrate the precise dose that he/she requires.

The use of cannabis as a medicine continues to be illegal as far as the federal government is concerned despite the fact that 23 states have now approved its medical use for specified symptoms and syndromes; and there is every expectation that before long this will be the case in a significant majority of states. But because states arrogate to themselves the decisions about which symptoms and syndromes are allowed to be treated with marijuana, its legal availability as a medicine varies greatly from state to state. In some states, like New Jersey, its use as a medicine is so restrictive that few patients are able to avail themselves of it. On the other hand, while the regulations in California are much more liberal in allowing a wider variety of symptoms and syndromes which can be legally treated with cannabis, this also makes it easier to acquire by people who want to use it for purposes the authorities do not approve of. And given the large and growing number of medical uses for which cannabis can provide relief, it would be difficult if not impossible to codify them in regulations. In terms of its overall therapeutic utility, marijuana is at least as useful as aspirin; cannabis has both a broader therapeutic spectrum and a smaller risk of significant toxicity.

EXHIBIT 5

The present frustration that legal herbal cannabis is not medically generally available has some parallels to the history of the availability in the United States of lithium carbonate as a therapeutic in the treatment of bipolar disorder. In 1948, Dr. John Cade, an Australian psychiatrist, made a most important medical contribution when he discovered that lithium carbonate was a very useful mood stabilizer in the treatment of bipolar disorder. In the absence of any other drug which would as effectively deal with episodes of mania, the publication of this discovery was greeted with great enthusiasm. At the time there were few treatments available to patients with bipolar disorder and most were treated with antipsychotics, electroconvulsive therapy or lobotomy. Elsewhere in the world where it attracted a great deal of attention as the first drug which could be effective in the treatment of this disorder, lithium carbonate soon became available to psychiatrists and their patients, but not in the United States, causing considerable frustration to American psychiatrists and the unnecessarily prolonged suffering of patients and their families. It did not become available for prescription in the United States until 1970.

The enormous potential of lithium salt as a psychiatric therapeutic was, of course, known to the U.S. pharmaceutical industry from the time Cade published his ground-breaking paper in 1949. However, because it is a naturally-occurring substance and as such could not be patented, the pharmaceutical industry saw it as having no commercial value. Eventually the United States government, through its Orphan Drug Act, supported the testing that was essential for FDA approval. Its approval in 1970 made it possible for it to finally appear on the market in the United States. It was immediately adopted by allopathic medicine as a valuable drug in the treatment of bipolar disorder.

Inevitably, the number of states which have decided to ignore the federal government's *Reefer Madness* view of cannabis and have allowed marijuana to be legally available as a medicine will continue to grow; and just as certainly so will the number of states which, like Washington and Colorado, have abandoned prohibition altogether and substituted regulations for responsible adult use. At the present time, there is an uneasy detente which makes for a lot of uncertainty particularly for cannabinopathic patients and the owners of the dispensaries from which they buy their medicine. That the federal government should cling to its outdated notions of cannabis is difficult to understand.

The recent history of both the growth of interest and use of marijuana as a medicine and the extraordinary rise in the number of citizens who believe that marijuana should now be legalized (according to a 2013 Gallup poll, legalization is now supported by 58%, 10% higher than it was one year earlier) have so undermined the federal government's posture toward cannabis that it now appears inevitable that the prohibition will be repealed in the near future. It is possible that this will be preceded by the long overdue decision to free cannabis from Schedule I. Either of these events will make it legally possible to do the large double-blind controlled studies which are required for approval as a legal therapeutic by the FDA. However, there is some question as to whether they should or could be undertaken for several reasons. Physicians have always had available evidence of a different kind, whose value is often underestimated. Anecdotal evidence commands much less attention than it once did, yet it is the source of much of our knowledge of synthetic medicines as well as plant derivatives. As noted above, controlled experiments to determine both efficacy and toxicity were not needed to recognize the therapeutic potential of chloral hydrate, barbiturates, aspirin, curare, insulin, or penicillin. The anecdotal evidence which underlies the success of marijuana

as a medicine exceeds by at least an order of magnitude that which allowed the above-mentioned drugs admittance to the pharmacopeia. Furthermore, it is questionable whether these studies will be undertaken for lack of a sponsor to provide the enormous funds which would be necessary.. It seems unlikely that the federal government would, any time in the near future, be willing to take a lithium-like approach to herbal marijuana even after the prohibition has been repealed. The pharmaceutical industry will not undertake such an endeavor because it is impossible for them to patent marijuana and, in any event, it would be worthless after the repeal of the prohibition. The 23 states which have now accepted medicinal marijuana and the two which have made it available for any use have obviously been convinced by this mountain of anecdotal evidence that herbal marijuana is both safe and efficacious. Some may regard it as irresponsible to suggest on the basis of anecdotes that cannabis may help people with a variety of disorders. That might be a problem if marijuana were a dangerous drug, but we now know that it is remarkably safe.

Medicine, as it is practiced in the United States today, is synergistically related to the pharmaceutical industry. While in medical school, students' education in pharmacology has less to do with individual pharmaceutical products than it does with the principles of pharmacology. They learn much of what they know about specific pharmaceutical products in their post-medical school training in internships and residencies. They are introduced to new drugs through medical journals, both their papers and drug advertisements. Physicians are regularly visited by pharmaceutical company salespeople ("detail men or women") who provide them with formulaic accounts of the usefulness of a particular pharmaceutical and samples of the new drug along with other pharmaceuticals they may personally desire . They also provide many physicians with gifts, such as golfing fees, travel expenses and even money.

At the present time and for the foreseeable future herbal marijuana and its products are the gold standard of cannabinopathic medicine. Let us consider what might be involved in integrating it into allopathic medicine at this time. The first requirement is that the FDA approve herbal marijuana as a medicine. One can argue, however, that FDA approval is superfluous where cannabis as a medicine is concerned. Drugs must undergo the above-described rigorous, expensive, and time-consuming tests before being granted FDA approval for marketing as medicines. The purpose is to protect the consumer by establishing safety and efficacy, to regulate the commercial distribution of drug company products, and to protect the public against false or misleading claims about their efficacy and safety. The drug is generally a single synthetic chemical the pharmaceutical company has acquired or developed and patented. It submits an application to the FDA and tests it, first for safety in animals and then for clinical safety and efficacy. The company must present evidence from double-blind controlled studies demonstrating that the drug is more effective than a placebo. Case reports, expert opinion, and clinical experience are not considered sufficient. But there is considerable doubt whether the FDA rules should apply to cannabis as there is no question regarding its safety. Thousands of years of experience have demonstrated its medical value, and government efforts through the National Institute of Drug Abuse to establish a level of toxicity sufficient to support its prohibition have instead provided a record of its safety.

Even if it were legally and practically possible to conduct the various phased studies to win FDA approval, where would the money to finance the studies come from? New medicines are almost invariably introduced by drug companies that spend many millions of dollars on the development of each product. They are willing to undertake these

costs only because of the large profits they anticipate during the 20 year they own the patent, and marijuana cannot be patented. For this and other reasons it is unlikely that the pharmaceutical industry will ever develop herbal marijuana as an officially recognized medicine via this route. It is not even necessary to establish this kind of certification; the modern FDA protocol is not needed to establish a risk-benefit estimate for a drug with the therapeutic history of marijuana. To impose this protocol on cannabis would be like making the same demand of aspirin, which was accepted as a medicine more than 60 years before the advent of the double-blind controlled study. Many years of experience have demonstrated that aspirin has many uses and limited toxicity, yet today it could not be marshaled through the FDA approval process. Since the patent has long since expired there is no incentive to underwrite the substantial cost of this modern seal of approval. Other reasons for doubting the possibility of official approval include today's antismoking climate and most importantly, the widespread use of cannabis for purposes that lack government approbation.

To understand some of the obstacles to this approach, consider the effects of granting marijuana legitimacy as a medicine while prohibiting it for any other use. Imagine that somehow the FDA approved herbal marijuana for the treatment of Crohn's disease (the "labeled use") affirming that cannabis is safe and effective as a treatment for this disease and physicians are then allowed to prescribe it for this condition. This would present unique problems for the DEA, which is charged with monitoring the use of psychoactive drugs, because when a drug is approved for one medical condition, physicians are generally free to write "off-label" prescriptions – – that is, to prescribe it for other conditions as well. Knowledgeable physicians would want to prescribe it for some patients who suffered from multiple sclerosis, migraine headaches, compulsive disorders, Tourette's syndrome, spastic symptoms, depression, premenstrual syndrome and many other conditions for which the use of marijuana is well-established by a plethora of anecdotal evidence. They are also free to prescribe it for "conditions" for which there is little or no evidence of efficacy.

If the benefit of a drug is very large and the risk very small, the medicine is distributed "over-the-counter" (OTC). These drugs are considered so useful and safe that patients are allowed to use their own judgment without a physician's permission or advice. Thus, today anybody can buy and use aspirin for any purpose. This is permissible because aspirin is considered extremely safe; it takes "only" 1000 to 2000 lives a year in the United States. One can also purchase remarkably versatile drugs such as ibuprofen (Advil) and other non-steroidal anti-inflammatory drugs (NSAIDs) OTC as well, because they are considered safe; "only" about 10,000 Americans lose their lives to this class of drugs annually. Acetaminophen (Tylenol), another useful OTC drug, is responsible for about 10% of cases of end-stage renal disease. The public is allowed to purchase many herbal remedies whose dangers and efficacy remain unaddressed. Comparing these drugs with marijuana today, there is no doubt that it is a remarkably safe drug and if it regains its place in the official pharmacopeia it would rank as a serious contender for the title of least toxic substance in that compendium.

Then there is the question of who will provide the cannabis. The federal government now provides marijuana from its farm in Mississippi to the two surviving patients covered by the now-discontinued Compassionate IND program. Surely the government could not and would not produce marijuana for the many thousands of patients who need it, any more than it does for other prescription drugs. If production is contracted out, will the farmers have to enclose their fields with security fences and protect them

with security guards? How will the marijuana be distributed; if through pharmacies how would they provide secure facilities capable of keeping fresh supplies? Would the government need to control the price of pharmaceutical marijuana: not too high lest patients are tempted to buy it on the street or grow their own; not too low lest people with marginal or fictitious "medical" conditions beseech their doctors for prescriptions? What about the parallel problems with potency? When urine tests are demanded of workers, what would emerge as the bureaucratic and other costs of identifying those who use marijuana legally as a medicine, as distinguished from those who use it for other purposes?

To realize the full potential of cannabis as a medicine within the setting of the present prohibition, one would have to address all these problems and more. A delivery system that would successfully navigate this minefield would prove cumbersome, inefficient, and bureaucratically top-heavy. Government and licensing boards would insist on tight restrictions, challenging physicians as though cannabis were a dangerous drug every time is used for any new patient or purpose. Constant conflict would exist, with one of two outcomes: patients would not receive all the benefits they should, or they would obtain the benefits by abandoning the legal system for the black market or their own gardens and closets.

Meanwhile, a number of drug companies, attracted by the obvious medicinal properties of marijuana, are pursuing what one might refer to as the "pharmaceuticalization" of marijuana, the development of synthetic prescription drugs derived from cannabis: isolated individual cannabinoids; synthetic cannabinoids; and cannabinoid -analogs. The question is whether these developments will make herbal marijuana medically obsolete. Many of these new products may prove useful and safe enough for commercial development. It is uncertain, however, whether pharmaceutical companies will find them worth the enormous developmental costs given that they will have to compete with herbal marijuana. However, some may prove worthwhile – – for example, an inverse agonist that reduces appetite (the opposite of the marijuana effect called the "munchies") might be highly lucrative – – but for most specific symptoms, analogs or combinations of analogs are unlikely to emerge as more useful, less costly and safer than natural cannabis.

In the end, the commercial success of any pharmaceutical industry cannabinoid product will depend on how vigorously the prohibition against marijuana is enforced. It is safe to predict that the new analogs and extracts would cost much more than whole smoked or ingested marijuana, even at the inflated prices imposed by the prohibition tariff. It is doubtful that pharmaceutical companies would seem interested in developing these products if they have to compete with natural marijuana on a level playing field. The most common reason for using Marinol or Sativex is the illegality of marijuana, and many patients choose to ignore the law for reasons of efficacy and costs. The number of arrests on marijuana charges has steadily increased, yet patients continue to use smoked marijuana as a medicine. One wonders whether any level of enforcement would compel enough compliance with the law to embolden drug companies to commit the many millions of dollars it would take to develop new cannabinoid products. Pharmaceutical companies may develop some useful cannabinoid products, but it is unlikely that this pharmaceuticalization will displace natural marijuana for most medical purposes.

It is also clear that the realities of human need are incompatible with the demand for a

legally enforceable distinction between medicine and all other uses of cannabis. Marijuana use simply does not conform to the conceptual boundaries established by 20th century institutions. It enhances many pleasures and it has many medical uses, but even these two categories are not the only relevant ones. The kind of therapy often used to ease everyday discomforts does not fit any such scheme. In many cases, what lay people do in prescribing marijuana for themselves is not very different from what physicians do when they provide prescriptions for psychoactive or other drugs. The only workable way of realizing the full potential of this remarkable substance, including its full medical potential, is to free it from the dual set of regulations: those which control prescription drugs in general and the special criminal laws that control psychoactive substances. These mutually reinforcing laws establish a set of social categories that strangle marijuana's uniquely multifaceted potential. The only way out is to cut the knot by giving marijuana the same status as alcohol; legalizing it for adults for all uses, and removing it entirely from both the medical and criminal control systems.

In the face of the ongoing prohibition and the standoffish attitude of allopathic medicine, cannabinopathic medicine will continue to grow and develop. It will continue to collect data to help it discover new medicinal uses; to develop new strains to more effectively target particular symptoms and illnesses; to generate new modifications of herbal products to facilitate topical application, ingestion and smoking or vaporization; and it will continue to train people in the newest and best ways to use these products. In states which have not legalized the use of cannabis as a medicine, all aspects of the practice of cannabinopathic medicine will continue to be subterranean. In the states which have already made it more or less legally available as a medicine (depending on the comprehensiveness of the list of symptoms and syndromes for which the state allows it to be used) cannabinopathic practice continues to be only partially transparent. Because it is unlikely that any state will ever include such problems as pre-menstrual syndrome or intractable hiccups, for example, as indications for which cannabis may be useful, patients suffering from these and many other disorders will have to continue to use cannabis covertly or wait until after the prohibition comes to an end, as it recently has in Colorado and Washington. This is consistent with my belief that it will be impossible to realize the full potential of this plant as a medicine, not to speak of the other ways in which it is useful, in the setting of prohibition.

Two powerful forces are now colliding: the growing acceptance of cannabinopathic medicine and the proscription against any use of the plant marijuana, medical or non-medical. As a result, two distribution systems will emerge for medical cannabis: the conventional model of pharmacy-filled prescriptions for FDA-approved cannabinoid medicines, and a model closer to the distribution of alternative herbal medicines. The only difference, albeit an enormous one, will be the continued illegality of whole smoked or ingested cannabis. In any case, increasing medical use by either distribution pathway will inevitably make a great number of people familiar with cannabis and its derivatives. As they learn that its harmfulness has been greatly exaggerated and its usefulness under- estimated, the pressure will increase for drastic changes in the way that we as a society deal with this drug.

EXHIBIT 6

Introduction to the Endocannabinoid System

Dustin Sulak, DO Healer.com

As you read this review of the scientific literature regarding the therapeutic effects of cannabis and cannabinoids, one thing will become quickly evident: cannabis has a profound influence on the human body. This one herb and its variety of therapeutic compounds seem to affect every aspect of our bodies and minds. How is this possible?

At our integrative medical clinics in Maine and Massachusetts, my colleagues and I treat over 18,000 patients with a huge diversity of diseases and symptoms. In one day I might see cancer, Crohn's disease, epilepsy, chronic pain, multiple sclerosis, insomnia, Tourette syndrome and eczema, just to name a few. All of these conditions have different causes, different physiologic states, and vastly different symptoms. The patients are old and young. Some are undergoing conventional therapy. Others are on a decidedly alternative path. Yet despite their differences, almost all of my patients would agree on one point: cannabis helps their condition.

As a physician, I am naturally wary of any medicine that purports to cure-all. Panaceas, snake-oil remedies, and expensive fads often come and go, with big claims but little scientific or clinical evidence to support their efficacy. As I explore the therapeutic potential of cannabis, however, I find no lack of evidence. In fact, I find an explosion of scientific research on the therapeutic potential of cannabis, more evidence than one can find on some of the most widely used therapies of conventional medicine.

EXHIBIT 6

At the time of this writing (February 2015), a PubMed search for scientific journal articles published in the last 20 years containing the word "cannabis" revealed 8,637 results. Add the word "cannabinoid," and the results increase to 20,991 articles. That's an average of more than two scientific publications per day over the last 20 years! These numbers not only illustrate the present scientific interest and financial investment in understanding more about cannabis and its components, but they also emphasize the need for high quality reviews and summaries such as the document you are about to read.

How can one herb help so many different conditions? How can it provide both palliative and curative actions? How can it be so safe while offering such powerful effects? The search to answer these questions has led scientists to the discovery of a previously unknown physiologic system, a central component of the health and healing of every human and almost every animal: the endocannabinoid system.

What Is The Endocannabinoid System?

The endogenous cannabinoid system, named after the plant that led to its discovery, is perhaps the most important physiologic system involved in establishing and maintaining human health. Endocannabinoids and their receptors are found throughout the body: in the brain, organs, connective tissues, glands, and immune cells. In each tissue, the cannabinoid system performs different tasks, but the goal is always the same: homeostasis, the maintenance of a stable internal environment despite fluctuations in the external environment.

Cannabinoids promote homeostasis at every level of biological life, from the sub-cellular, to the organism, and perhaps to the community and beyond. Here's one example: autophagy, a process in which a cell sequesters part of its contents to be self-digested and recycled, is mediated by the cannabinoid system. While this process keeps normal cells alive, allowing them to maintain a balance between the synthesis, degradation, and subsequent recycling of cellular products, it has a deadly effect on malignant tumor cells, causing them to consume themselves in a programmed cellular suicide. The death of cancer cells, of course, promotes homeostasis and survival at the level of the entire organism.

Endocannabinoids and cannabinoids are also found at the intersection of the body's various systems, allowing communication and coordination between

different cell types. At the site of an injury, for example, cannabinoids can be found decreasing the release of activators and sensitizers from the injured tissue, stabilizing the nerve cell to prevent excessive firing, and calming nearby immune cells to prevent release of pro-inflammatory substances. Three different mechanisms of action on three different cell types for a single purpose: minimize the pain and damage caused by the injury.

The endocannabinoid system, with its complex actions in our immune system, nervous system, and all of the body's organs, is literally a bridge between body and mind. By understanding this system we begin to see a mechanism that explains how states of consciousness can promote health or disease.

In addition to regulating our internal and cellular homeostasis, cannabinoids influence a person's relationship with the external environment. Socially, the administration of cannabinoids clearly alters human behavior, often promoting sharing, humor, and creativity. By mediating neurogenesis, neuronal plasticity, and learning, cannabinoids may directly influence a person's open-mindedness and ability to move beyond limiting patterns of thought and behavior from past situations. Reformatting these old patterns is an essential part of health in our quickly changing environment.

What Are Cannabinoid Receptors?

Sea squirts, tiny nematodes, and all vertebrate species share the endocannabinoid system as an essential part of life and adaptation to environmental changes. By comparing the genetics of cannabinoid receptors in different species, scientists estimate that the endocannabinoid system evolved in primitive animals over 600 million years ago.

While it may seem we know a lot about cannabinoids, the estimated twenty thousand scientific articles have just begun to shed light on the subject. Large gaps likely exist in our current understanding, and the complexity of interactions between various cannabinoids, cell types, systems and individual organisms challenges scientists to think about physiology and health in new ways. The following brief overview summarizes what we do know.

Cannabinoid receptors are present throughout the body, embedded in cell membranes, and are believed to be more numerous than any other receptor system. When cannabinoid receptors are stimulated, a variety of physiologic processes ensue. Researchers have identified two cannabinoid receptors: CB1, predominantly present in the nervous system, connective tissues, gonads,

glands, and organs; and CB2, predominantly found in the immune system and its associated structures. Many tissues contain both CB1 and CB2 receptors, each linked to a different action. Researchers speculate there may be a third cannabinoid receptor waiting to be discovered.

Endocannabinoids are the substances our bodies naturally make to stimulate these receptors. The two most well understood of these molecules are called anandamide and 2-arachidonoylglycerol (2-AG). They are synthesized on-demand from cell membrane arachidonic acid derivatives, have a local effect and short half-life before being degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).

Phytocannabinoids are plant substances that stimulate cannabinoid receptors. Delta-9-tetrahydrocannabinol, or THC, is the most psychoactive and certainly the most famous of these substances, but other cannabinoids such as cannabidiol (CBD) and cannabinol (CBN) are gaining the interest of researchers due to a variety of healing properties. Most phytocannabinoids have been isolated from *cannabis sativa*, but other medical herbs, such as *echinacea purpura*, have been found to contain non-psychoactive cannabinoids as well. Interestingly, the cannabis plant also uses THC and other cannabinoids to promote its own health and prevent disease. Cannabinoids have antioxidant properties that protect the leaves and flowering structures from ultraviolet radiation - cannabinoids neutralize the harmful free radicals generated by UV rays, protecting the cells. In humans, free radicals cause aging, cancer, and impaired healing. Antioxidants found in plants have long been promoted as natural supplements to prevent free radical harm.

Laboratories can also produce cannabinoids. Synthetic THC, marketed as dronabinol (Marinol), and nabilone (Cesamet), a THC analog, are both FDA approved drugs for the treatment of severe nausea and wasting syndrome. Some clinicians have found them helpful in the off-label treatment of chronic pain, migraine, and other serious conditions. Many other synthetic cannabinoids are used in animal research, and some have potency up to 600 times that of THC.

Cannabis, The Endocannabinoid System, And Good Health

As we continue to sort through the emerging science of cannabis and cannabinoids, one thing remains clear: a functional cannabinoid system is essential for health. From embryonic implantation on the wall of our mother's uterus, to nursing and growth, to responding to injuries, endocannabinoids help

us survive in a quickly changing and increasingly hostile environment. As I realized this, I began to wonder: can an individual enhance his/her cannabinoid system by taking supplemental cannabis? Beyond treating symptoms, beyond even curing disease, can cannabis help us prevent disease and promote health by stimulating an ancient system that is hard-wired into all of us?

I now believe the answer is yes. Research has shown that small doses of cannabinoids from cannabis can signal the body to make more endocannabinoids and build more cannabinoid receptors. This is why many first-time cannabis users don't feel an effect, but by their second or third time using the herb they have built more cannabinoid receptors and are ready to respond. More receptors increase a person's sensitivity to cannabinoids; smaller doses have larger effects, and the individual has an enhanced baseline of endocannabinoid activity. I believe that small, regular doses of cannabis might act as a tonic to our most central physiologic healing system.

Many physicians cringe at the thought of recommending a botanical substance, and are outright mortified by the idea of smoking a medicine. Our medical system is more comfortable with single, isolated substances that can be swallowed or injected. Unfortunately, this model significantly limits the therapeutic potential of cannabinoids.

Unlike synthetic derivatives, herbal cannabis may contain over one hundred different cannabinoids, including THC, which all work synergistically to produce better medical effects and less side effects than THC alone. While cannabis is safe and works well when smoked, many patients prefer to avoid respiratory irritation and instead use a vaporizer, cannabis tincture, or topical salve. Scientific inquiry and patient testimonials both indicate that herbal cannabis has superior medical qualities to synthetic cannabinoids.

In 1902 Thomas Edison said, "There were never so many able, active minds at work on the problems of disease as now, and all their discoveries are tending toward the simple truth that you can't improve on nature." Cannabinoid research has proven this statement is still valid.

So, is it possible that medical cannabis could be the most useful remedy to treat the widest variety of human diseases and conditions, a component of preventative healthcare, and an adaptive support in our increasingly toxic, carcinogenic environment? Yes. This was well known to the indigenous medical systems of ancient India, China, and Tibet, and as you will find in this

report, is becoming increasingly well known by Western science. Of course, we need more human-based research studying the effectiveness of cannabis, but the evidence base is already large and growing constantly, despite the DEA's best efforts to discourage cannabis-related research.

Does your doctor understand the benefit of medical cannabis? Can he or she advise you in the proper indications, dosage, and route of administration? Likely not. Despite the two largest U.S. physician associations (American Medical Association and American College of Physicians) calling for more research, the U.S. Congress prohibiting federal interference in states' medical cannabis programs, a 5,000 year history of safe therapeutic use, and a huge amount of published research, most doctors know little or nothing about medical cannabis.

This is changing, in part because the public is demanding it. People want safe, natural and inexpensive treatments that stimulate our bodies' ability to self-heal and help our population improve its quality of life. Medical cannabis is one such solution. This summary is an excellent tool for spreading the knowledge and helping to educate patients and healthcare providers on the scientific evidence behind the medical use of cannabis and cannabinoids.